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INFORMATION

UPON SUCH SUBJECTS AS ACUTE RHEUMATIC FEVER, ACUTE AND CHRONIC ARTHRITIS, COMMON COLD, GOUT, AND THE RELIEF OF SUCH CONDITIONS AS MYOSITIS AND NEURITIS, WILL BE FURNISHED BY US UPON REQUEST FROM CLINICIANS. MEDICAL REPRINTS AND ABSTRACTS ARE CONVINCING TESTIMONY WHEN ADDUCED IN FAVOR OF A WELL-KNOWN THERAPEUTIC GROUP.

Pharmaceutical Division

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ERRATA

VOLUME XLVI, NO. 1, JANUARY, 1930

Page 10, line 11: "Professor of the School of Medicine" should read *Professor of the History of Medicine.*

Page 98, line 15: "Money" should read *Memory.*

THE RACE AND SEX DISTRIBUTION OF THE LESIONS OF SYPHILIS IN 10,000 CASES[1,2]

THOMAS B. TURNER, M.D.

From the Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital

It has seemed that information of interest might be gleaned from a comprehensive study of the race and sex incidence of the lesions of syphilis in a large series of patients. The monumental statistical studies of the elder Fournier (1) have not been repeated since the discovery of the Wassermann reaction, nor in a population of two races such as whites and negroes.

This paper is not concerned with the race and sex incidence of syphilis in the general population, since a vast amount of information is readily available on this point, but with the incidence of the various manifestations of syphilis in a known syphilitic population. The statistics are based on the race and sex distribution of the lesions of syphilis among 11,818 consecutive admissions to the Syphilis Clinic of the Johns Hopkins Hospital. Of these patients, 10,000 were syphilitics studied in sufficient detail to permit an accurate diagnosis, 996 were non-syphilitic and in 822 the diagnostic study was incomplete. This clinic receives for study all ambulatory patients, with the exception of children under 12 years of age, with recognized or suspected syphilis admitted to the Johns Hopkins Hospital; a complete diagnostic survey of each patient is made, and the diagnoses are recorded in accordance with a uniform system of nomenclature. A spinal fluid examination has been obtained in a high proportion of cases. The frequent use of the Wassermann test in other clinics of the hospital, several of which use it routinely, discloses in many patients the presence of syphilis when it would otherwise be unrecognized.

[1] This investigation was aided by a grant from the Committee on Research in Syphilis.

[2] Zimmermann, in 1921 (*Arch. Derm. and Syph.*), published a similar paper from the clinic based on 1,843 cases all of which are included in this paper.

Table I shows the race and sex distribution of the total cases of syphilis. Baltimore has a population of 717,068 whites and 124,660 negroes (estimated census of 1929); practically all of the latter belong to the dispensary class of patients. Statistics compiled by Keidel and Moore (2) show an incidence of positive blood Wassermann reactions, among approximately 5,000 patients admitted to the public medical wards of the Johns Hopkins Hospital, of 7.6 per cent in whites and 22.9 per cent in negroes. Of 4,000 consecutive medical discharges 9.7 per cent of the whites and 25.4 per cent of the negroes were diagnosed as syphilitic. Paullin and others (3), in a study of an adult negro hospital population in Atlanta, Ga., estimated the incidence of syphilis as 20 per cent. It is inevitable, then, that any

TABLE I

Race and sex distribution of 10,000 cases of syphilis

White males	2,213
White females	1,225
Total white	3,438
Colored males	2,804
Colored females	3,758
Total colored	6,562
Total males	5,017
Total females	4,983

general hospital in this part of the United States will be called upon to treat a great number of negroes with syphilis and it is not surprising that over 65 per cent of our total cases belong to that race. In regard to sex, however, the number of males and females is almost equal.

No attempt will be made to publish a detailed report on the occurrence by years of the various syphilitic lesions, but it may be of interest to note the total race and sex incidence by years, in order to determine whether or not there has been any significant variation.

In Charts 1 and 2 is given the incidence, respectively, of all patients, and of patients with early syphilis only, the latter, of course, representing recent infections. The similarity of the curves for each group in the two charts strongly suggests that the variation in the incidence

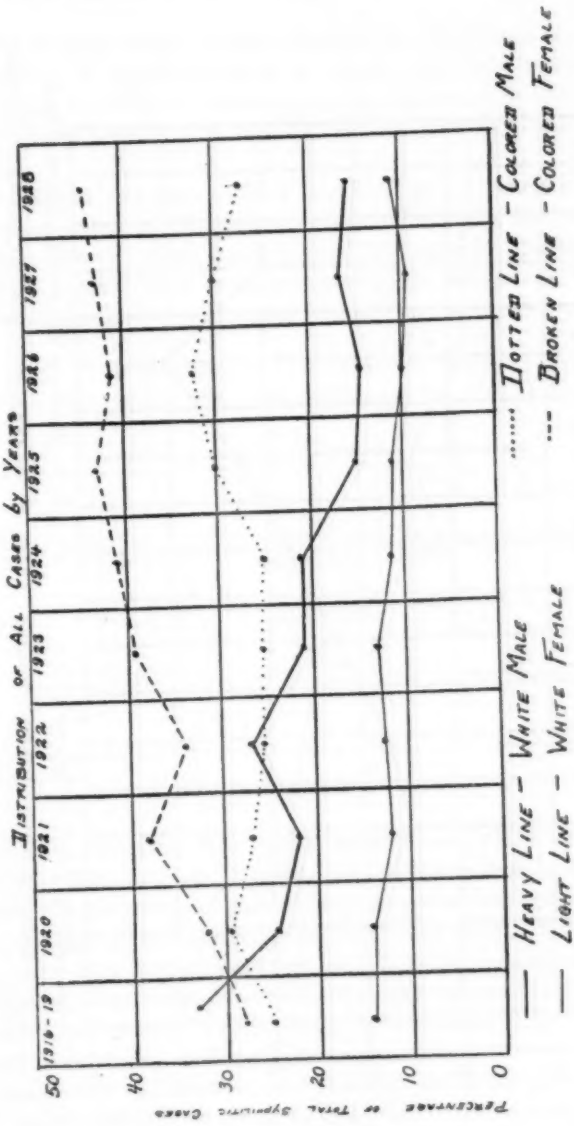
Distribution of All Cases by Years
1918-19
1920
1921
1922
1923
1924
1925
1926
1927
1928
50
40
30
20
10
0
Percentage of Total Syphilitic Cases
—— Heavy Line – White Male
—— Light Line – White Female
..... Dotted Line – Colored Male
--- Broken Line – Colored Female

CHART 1

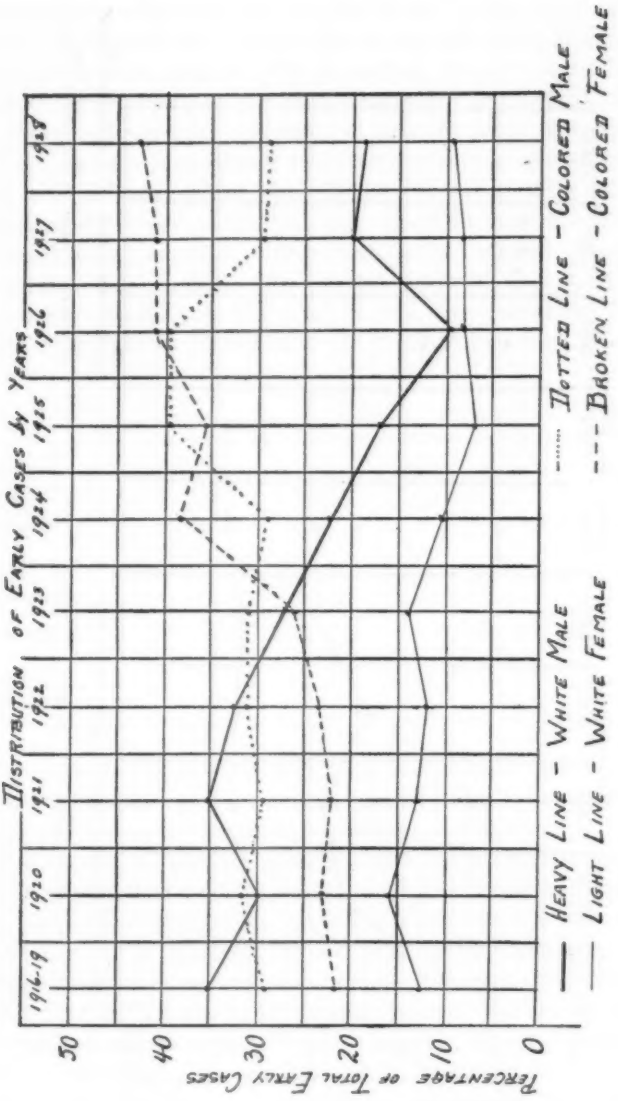
Distribution of Early Cases by Years
1916-19
1920
1921
1922
1923
1924
1925
1926
1927
1928
Percentage of Total Early Cases
50
40
30
20
10
0
Heavy Line - White Male
Light Line - White Female
Dotted Line - Colored Male
Broken Line - Colored Female

CHART 2

in the total cases is due, in large measure, to a significant decrease in the number of recent infections in whites, especially white males. The curves in Chart 3, representing the incidence in the various groups of the patients with late syphilis only, show no such yearly change.

Our material has been divided into four groups representing the four major stages of the disease—congenital syphilis, early syphilis, late syphilis with lesions (tertiary) and late syphilis without lesions (latent). A fifth group is made up of those patients on whom a positive diagnosis of syphilis could be made, but in whom some doubt

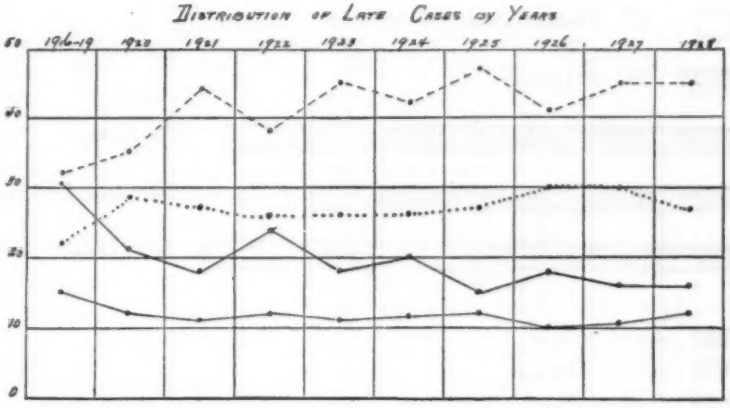

CHART 3

existed as to the nature of the pathological process which was present. These have been listed as "Proved, stage undetermined." In Chart 4 is shown the percentage of each of these groups in the total number of cases, and also the race and sex incidence in each group. It is interesting to note that each of the three major groups of acquired syphilis is composed of approximately one third of the total number of patients. The other two groups, "Proved, stage undetermined" and congenital, comprise a relatively small proportion of the total.

Proved—stage undetermined. One hundred and thirty-three patients with positive blood Wassermann reactions were included in this

group, most of whom also presented some lesion which may have been syphilitic. The most confusing lesions were those of the lip and leg, where carcinoma in the former, and varicose ulcer in the latter, had to be differentiated from gumma. The diagnostic difficulty arose chiefly from the failure of such patients to return for observation after a therapeutic test. A few patients with aortic regurgitation, a positive Wassermann reaction and a history of rheumatic fever also offered considerable difficulty in diagnosis from an etiological standpoint. This group is so small that the race and sex incidence is unimportant.

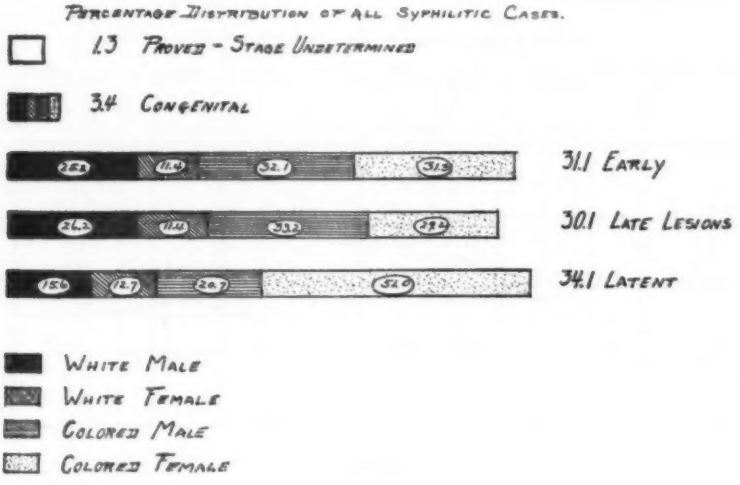

Chart 4

Congenital. Children under 12 years of age are not treated in this clinic, so that our experience with congenital syphilis has been comparatively limited and this material is of little statistical value. Of the 343 patients in this group, 25.3 per cent were white males, 26.5 per cent white females, 16.5 per cent colored males, and 31.7 per cent colored females.

Early syphilis. There were 3104 patients who exhibited some lesion of early syphilis (*i.e.*, chancre); such manifestations of a secondary type, as skin, eye, or bone lesions; or acute meningitis or recurrent

secondary syphilis of the skin, mucous membrane, eye, or central nervous system. Those patients who on admission had both a chancre and secondary skin lesions were classified as early secondary syphilis and were not listed under the primary stage. Table II shows the number and percentage of cases in each race and sex group based on the total number of cases of early syphilis in the respective groups. That the percentages do not total 100 is accounted for by the fact that a number of patients with recurrent secondary syphilis had been previously treated in the clinic and hence were not included in the total number.

TABLE II

Comparative incidence of lesions of early syphilis

RACE AND SEX	PRIMARY		SECONDARY		SECONDARY RECURRENT		TOTAL EARLY
	Number	Per Cent	Number	Per Cent	Number	Per Cent	
White males	250	32.0	486	62.0	106	13.5	783
White females	22	6.4	313	91.2	39	11.3	343
Colored males	261	26.0	700	70.0	92	9.2	1,001
Colored females	48	4.9	914	93.5	72	7.3	977
White	272	24.1	799	70.9	145	12.8	1,126
Colored	309	15.5	1,614	81.5	164	8.2	1,978
Males	511	28.6	1,186	66.4	198	11.1	1,784
Females	70	5.3	1,227	92.9	111	8.2	1,320

Primary syphilis. Genital chancres are rarely observed in females. This is probably due to the fact that the chancre occurs in some unexposed portion of the genital tract. Since it has been proved experimentally (4), however, that animals may be infected with syphilis without the appearance of a lesion at the portal of entry, it is highly probable that man may also, at times, be infected in a similar manner. We are impressed repeatedly by the number of persons, males as well as females, who show evidence of syphilis, early or late, yet who can give no history of an initial lesion.

Primary lesions have been further divided, as shown in Table III, into two classes. Since 1921, chancres have been classified as "sero-

TABLE III

Primary syphilis—race and sex distribution of lesions with percentage based on total early cases for each race and sex group

	WHITE MALES		WHITE FEMALES		COLORED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1 Undifferentiated	66	8.4	4	1.2	52	5.2	15	1.5	70	6.2	67	3.4	118	6.6	19	1.4	137	4.4
1 Sero-negative	94	12.0	6	1.7	68	6.8	10	1.0	100	8.8	78	3.9	162	9.0	16	1.2	178	5.4
1 Sero-positive	90	11.4	12	3.5	141	14.1	23	2.4	102	9.1	164	8.2	231	13.0	35	2.7	266	8.6
Total	250	31.8	22	6.4	261	26.1	48	4.9	272	24.1	309	15.5	511	28.6	70	5.3	581	18.6
1 Extragenital	24	3.0	16	4.6	11	1.1	13	1.3	40	3.5	24	1.2	35	1.9	29	2.2	64	2.0
Reinfection	24		2		6		2		26		8		30		4		34	

TABLE IV

Incidence of special lesions in secondary syphilis (based on percentage of total cases of secondary syphilis in each group)

	WHITE MALES		WHITE FEMALES		COLORED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Eye	17	3.5	6	1.9	67	9.5	44	4.8	23	2.9	111	6.8	84	7.0	50	4.0	134	5.5
Skeletal	2	0.4	2	0.6	22	3.1	16	1.7	4	0.5	38	2.2	24	2.0	18	1.5	42	1.7
Nephritis	1	0.1	1	0.3	2	0.3	4	0.4	2	0.2	6	0.4	3	0.2	5	0.4	8	0.3
Malignant	4	0.8	1	0.3	3	0.4	3	0.3	5	0.6	6	0.4	7	0.6	4	0.3	11	0.4
Sero-negative	3	0.6	0	0	9	1.3	4	0.4	3	0.4	13	0.8	12	1.0	4	0.3	16	0.6
Acute meningitis	31	6.4	9	2.8	22	3.1	16	1.7	40	5.0	38	2.3	53	4.4	25	2.0	78	3.2
Total secondary	486		313		700		914		799		1,614		1,186		1,227		2,413	

negative" and "sero-positive" according to the state of the blood Wassermann reaction on the day of observation; prior to that time no distinction into classes was made and all primary lesions were listed as "undifferentiated." As shown by Stokes and McFarland (5), the blood Wassermann is positive in 70 per cent of patients by the end of the second week after the appearance of the chancre, so that our present classification indicates roughly the duration of the lesion. A slightly higher percentage of white males with early syphilis came under observation during the primary stage than did colored males, and a much higher proportion of the former are seen in the sero-negative phase of primary syphilis. This has a direct bearing on the results of treatment (6) and is no doubt influenced to a great extent by the social status and intelligence of the patient. A study of this material by years reveals that there has been no essential change in the incidence of sero-negative and sero-positive primary syphilis since 1921, although Harrison (7), in Great Britain, has shown conclusively what can be done by education and provision of easily accessible treatment centers on the promptitude with which patients seek treatment. In one large treatment center, in 1921, in approximately one-fifth of all early cases the patients had applied for treatment in the sero-negative primary stage, whereas in 1927 the proportion had risen to over one-third of the total early cases.

Extra-genital chancres occurred nearly three times as frequently in whites as in negroes.

Reinfection. Halley and Wassermann (8), in an exhaustive review of the subject of reinfection, collected, out of approximately 700 reported cases, 229 which they felt were undoubted instances of a second infection, and to these they were able to add 8 cases from this clinic. In our total material we have 34 cases diagnosed as reinfection, and though only 8 fulfill the stringent criteria set up by Halley and Wassermann, yet it might be that the former figure represents the incidence of reinfection more closely than the latter; for their paper was an effort to study immunity to a second infection as exhibited in man, and in order to make their conclusions comparable to those drawn from experiments on laboratory animals, it was necessary that the evidence on which these conclusions were based should be above criticism. Consequently, many of our own cases, as

well as those reported elsewhere, were discarded by Halley and Wassermann for lack of absolute proof. The patients reported here as reinfections, therefore, do not represent absolutely proven cases, but ones in which this diagnosis is highly probable.

The lower incidence of reinfection in women is probably due to two factors; first, the liability of chancres to occur in parts not readily accessible to examination; second, the infrequency with which treatment is instituted during the primary stage. Studies on both man (8) and animals (9) have shown that the earlier treatment is begun the more likely is reinfection to occur. In most women, therefore, by the time treatment is instituted a certain degree of immunity has presumably developed; many men, on the other hand, receive treatment soon after their primary lesion has appeared, and, hence, before any useful degree of immunity has developed.

Secondary syphilis. In Table IV are shown the number and incidence of special lesions in secondary syphilis, the percentage being based on the total cases of early syphilis in the respective age and sex groups. The great majority of patients had skin lesions, and indeed most of those exhibiting some other lesion of secondary syphilis showed a skin rash as well. I have made no attempt to determine the incidence of the various types of secondary syphilitic rashes in the two races, but Zimmermann (10), reporting from this clinic on 507 of these patients with secondary syphilis, found that approximately 44 per cent of whites with skin lesions exhibited a macular rash, while among negroes papular, especially folliculo-papular and annular lesions, were by far the most frequent. No striking difference was noted between the sexes of the same race.

Eye. Acute affections of the ciliary tract are the commonest eye lesions of secondary syphilis, although lesions of the optic nerve, retina and choroid are observed with a frequency which varies according to the diligence and enthusiasm of the observer. The interpretation of slight changes occurring in the ocular tissues is often open to debate, so that for the purposes of this paper we have confined our diagnosis, aided by an ophthalmologist, to those lesions which are less equivocal. Negroes, especially negro males, were more prone than whites to develop acute iritis, but we have no accurate data bearing on the race and sex incidence of other eye lesions.

Skeletal. Many patients with secondary syphilis complain of bone and joint pains, but in only a few does the local pathological process reach the clinical threshhold in the form of a periostitis or arthritis. This occurred much more frequently in negroes than in whites—in nearly 5 to 1 in this series.

Nephritis. Acute syphilitic nephritis has been extremely rare in this clinic, there having been only 8 patients in whom the diagnosis was reasonably certain. In all of these the acute nephritis was associated with other manifestations of secondary syphilis, and, what we feel is most important, the institution of antisyphilitic treatment was followed by the prompt subsidence of the nephritis. The small number of patients with this affection renders race and sex comparison valueless.

Sero-negative. A negative blood Wassermann reaction in the presence of unmistakable untreated secondary syphilis is comparatively rare and we have had too few cases to justify any conclusions regarding the race and sex incidence.

Acute meningitis. While perhaps in a majority of all patients the central nervous system is invaded at the time of the general dissemination of organisms in the early stages of syphilis, in relatively few patients does the clinical or serological picture of an acute meningitis appear. We do not know what determining factor produces the symptoms of meningitis in one patient and not in another, but certainly where meningitis occurs early in the infection, race and sex differences are seen which are quite as pronounced as in the late stages of the disease.

The incidence of this affection in early syphilis is more than twice as high in whites as in negroes, and twice as high in males as in females.

The figures are especially significant, for, contrary to the belief previously held that the prognosis in cases of acute meningitis and of neurorecurrence is relatively good for the remote future, evidence is accumulating to show that the prognosis is grave unless the most efficient treatment is instituted (11, 12).

Recurrent secondary syphilis. This group includes only those patients who have received inadequate treatment for early syphilis—primary or secondary—and who within the first year again develop some syphilitic lesion. Table V shows the number of cases and incidence in this group of patients.

TABLE V

Incidence of recurrent secondary lesions (based on percentage of early cases in each group)

	WHITE MALES		WHITE FEMALES		COLORED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Cutaneous	46	5.8	19	5.5	39	3.9	29	3.0	65	5.7	68	3.4	85	4.7	48	3.6	133	4.2
Mucous membranes	18	2.3	5	1.4	17	1.7	22	2.2	23	2.0	39	1.9	35	1.9	27	2.0	62	2.0
Eye	7	0.9	3	0.9	10	1.0	11	1.1	10	0.9	21	1.1	17	0.9	14	1.0	31	1.0
Neuro-recurrent	35	4.4	12	3.5	26	2.6	10	1.0	47	4.1	36	1.8	61	3.4	22	1.6	83	2.6
Total recurrent	106	13.5	39	11.3	92	9.2	72	7.3	145	12.8	164	8.2	198	11.1	111	8.2	309	9.9
Total early	783		343		1,001		977		1,126		1,978		1,784		1,320		3,104	

TABLE VI

Types of lesions in late syphilis (percentage of total cases of late syphilis in each race and sex group)

	WHITE MALES		WHITE FEMALES		COLERED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Skin and mucous membranes	104	7.8	91	11.6	154	9.0	217	8.3	195	9.3	371	8.6	258	8.5	308	9.0	566	8.8
Bone	78	5.9	42	5.4	199	11.6	211	8.0	120	5.7	410	9.4	277	9.1	253	7.4	530	8.2
Joint	1	0.1—	3	0.4	17	1.0	17	0.6	4	0.2	34	0.7	18	0.6	20	0.6	38	0.6
Viscera	20	1.5	8	1.0	54	3.1	74	2.4	28	1.3	128	3.0	74	2.4	82	2.4	156	2.4
Eye	27	2.0	17	2.1	64	3.7	73	2.0	44	2.1	137	3.1	91	3.0	90	2.6	181	2.8
Gland	1	0.1—	1	0.1	13	0.7	18	0.6	2	0.1—	31	0.7	14	0.4	19	0.5	33	0.5
Upper respiratory tract	56	4.2	44	5.6	87	5.1	127	4.8	100	4.8	214	4.9	143	4.7	171	5.0	314	4.9
Cardio-vascular	115	8.7	38	4.8	306	17.9	190	7.2	153	7.2	496	11.4	421	13.9	228	6.7	649	10.1
Central nervous system	519	39.3	174	22.3	272	15.9	183	7.0	693	33.0	455	10.5	791	26.1	357	10.5	1,148	17.8
Latent	532	40.3	436	55.9	708	41.5	1,739	66.4	968	46.1	2,447	56.6	1,240	41.0	2,175	64.0	3,415	53.1
Total late	1,318		780		1,704		2,618		2,098		4,322		3,022		3,398		6,420	

Recurrences on the skin or mucous membranes seem to occur more often in whites than in negroes. In each race the lesions tend to be mild, and rarely diffuse, with a marked tendency to bizarre types.

Syphilitic affections of the eye, occurring after inadequate treatment, were not common, and occurred with equal frequency in each race and sex, but they are not apt to be innocuous lesions, for some of the most rapidly destructive eye lesions that we have seen have occurred in patients in this group.

Neurorecurrence. Neurorecurrence or neurorecidive, occurring more than three times more frequently in whites than in negroes, and in about the same relative proportion in males and females, seems to indicate, along with the figures for acute meningitis, that there is a profound difference in the vulnerability of the central nervous system of the sexes and the two races as regards infection with *Treponema pallidum*. A factor which no doubt influences these results is the percentage of patients in each race and sex group who lapse early in the course of treatment, and while we have no accurate data on this point I think it safe to say that probably no class of patients is more indifferent toward antisyphilitic treatment than the American negro. Were this taken into account, the difference in the two races would be even more marked. Our cases of neurorecurrence have been studied by Zimmermann (13) and Moore (11).

Late syphilis. Patients who on admission to the clinic were thought to have had their infection for two years or longer made up 64.2 per cent of all syphilitic cases. Of these 46.9 per cent exhibited some tertiary lesion and 53.1 per cent had no active lesion, the diagnosis being based on laboratory data. Table VI shows the number of patients manifesting each type of lesion, the percentage being based on the total number of cases of late syphilis. Several different types of late lesions were not infrequently seen in the same patient, and when such a condition occurred, each type of lesion was tabulated under its respective heading, while the case was tabulated as one total case. No effort has been made in this study to record the coincidental occurrence in the same patient of different types of lesions.

Skin and mucous membrane. There is no striking difference in the incidence of late syphilitic lesions of the skin and mucous membranes between male and female, or between white and negro patients. It

seems fair to say that the lesions in colored patients are more advanced and destructive than in whites. This is due probably to the tardiness with which the former seek treatment rather than to any racial difference.

Bone. Lesions of the naso-palatine bones are not included in this group, nor are lesions affecting primarily the joints. The former are described under "Upper Respiratory Tract" and the latter under the succeeding subtitle.

Negroes are considerably more prone to develop bone lesions than are whites, while males in general show a higher incidence than do females. The following tabulation shows the number of different bones involved in 325 patients in whom detailed information is available.

BONE	NUMBER	PER CENT
Tibia	161	49.5
Skull	54	16.6
Sternum	23	7.0
Clavicle	28	8.6
Sternoclavicular joint	27	8.3
Humerus	19	5.8
Forearm	17	5.2
Femur	11	3.3
Fibula	10	3.0
Ribs	8	2.4
Other (chiefly small bones of hands and feet, scapula and spine)	34	10.4

These figures represent the number of patients in whom involvement of a bone was detectable, for the most part clinically, and we feel quite certain that were a careful x-ray study made of all patients with late syphilis or of all patients presenting at least one clinically recognizable bone lesion many more syphilitic bone lesions would be discovered. Indeed, this has actually been our experience in a number of patients studied in the past year. Periostitis is the pathological process most frequently observed, especially in the long bones, while an osteitis is the most frequent process observed in the skull. In several of our patients a severe headache due to osteitis of the skull had been ascribed to a coexisting hypertension. The headache disappeared with the institution of anti-syphilitic treatment.

It is interesting that in all cases bone involvement was nearly as common as tertiary lesions of the skin and mucous membrane.

Joints. Syphilitic arthritis as a manifestation of late syphilis has been observed but rarely in this clinic, and a study of some of these patients by Chesney, Kemp, and Baetjer (15) showed that there were few clinical and roentgenological features to distinguish it from an arthritis of other etiology. *Treponema pallidum* was demonstrated in the joint fluid in a few cases, while in others a therapeutic test was necessary to establish the diagnosis.

The racial predisposition to the development of arthritis in early syphilis is also noticeable in late syphilis, for it is more common in negroes than in whites.

Syphilitic affections of the sternoclavicular joint have been included, arbitrarily perhaps, in the preceding group, and Charcot arthropathies have been tabulated under lesions of the central nervous system.

Viscera. The patients in this group are not suitable for detailed statistical study and consequently no tabulation will be made. In this group are placed patients with lesions of various viscera, such as the liver, rectum, salivary glands, testes and stomach. There were 34 patients with clinically recognizable syphilis of the liver and 51 patients with stricture of the rectum. The former were about equally divided among each race and sex, whereas the latter were almost exclusively colored females. In fact, syphilitic stricture of the rectum in white patients is one of the rarest of lesions and we have never seen it in a white man. Syphilitic orchitis has not been a frequent lesion in this clinic, and syphilis of the stomach has been proved beyond a reasonable doubt in only a few cases.

Eye. Affections of the uveal tract, choroid and retina, and vascular keratitis occur late in the course of a syphilitic infection as well as in early syphilis, and although the difference in incidence in the race and sex groups is not as striking as in early syphilis, colored men seem more prone than others to develop these lesions.

Primary optic atrophy and palsies of ocular muscles are not included under this heading.

Glands. Gummatous involvement of the lymph nodes is a comparatively uncommon condition but always an interesting one from the standpoint of differential diagnosis. Gumma of the lymph nodes

TABLE VII

Types of cardiovascular syphilis distributed according to race and sex, with their percentage based on total cases of late syphilis in the respective race and sex group

	WHITE MALES		WHITE FEMALES		COLORED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Aortitis	51	3.8	19	2.4	144	8.4	118	4.5	70	3.3	262	6.0	195	6.4	137	4.0	332	5.1
Aortic insufficiency	37	2.8	11	1.4	86	5.0	40	1.5	48	2.2	126	2.9	123	4.0	51	1.5	174	2.7
Angina	8	0.6	1	0.1	5	0.3	3	0.1	9	0.4	8	0.1	13	0.4	4	0.1	17	0.2
Aneurysm	17	1.2	3	0.3	51	3.0	18	0.7	20	0.9	69	1.6	68	2.2	21	0.6	79	1.2
Other	2	0.1	4	0.5	20	1.1	11	0.4	6	0.2	31	0.7	22	0.7	15	0.4	37	0.5
Total	115	8.7	38	4.8	306	17.9	190	7.2	153	7.2	496	11.4	421	13.9	228	6.7	649	10.1
Total late cases	1,318		780		1,704		2,618		2,098		4,322		3,022		3,398		6,420	

has occurred almost exclusively in negroes; the cervical lymph nodes are by far the most frequently involved, and the resemblance to tuberculous lymphadenitis is usually very striking. The diagnosis can usually be established only with the aid of a therapeutic test.

Upper respiratory tract. Lesions involving the nasal septum, hard and soft palate and pharyngeal wall are among the most characteristic of all syphilitic lesions and occur in frequency in the order given. There is no significant race or sex predilection for the development of these lesions.

Cardiovascular. Although patients with syphilitic involvement of the cardiovascular system are subdivided with respect to the main type of lesion which they present, it is realized that the underlying pathological process in the majority of patients is the same. Taking cardiovascular syphilis as a whole, it is seen that males of both races, and particularly negro males, are especially prone to this type of syphilis. The incidence among all late syphilitics was 10 per cent, whereas among colored males of all types the incidence of cardiovascular syphilis was 17.9 per cent as opposed to an incidence of 4.8 per cent among white females. Owing to the fact that white males showed a slightly higher incidence than colored females, it is assumed that, although race seems an important factor, it is not the sole one that determines the development of clinically recognizable cardiovascular lesions in the course of a syphilitic infection. Table VII shows the distribution of the cases in which this type of syphilis occurred.

Aortitis. This group comprised those patients who had the clinical picture of an aortitis, without aneurysm or aortic regurgitation. The findings on which this diagnosis was based were those described, in this country, chiefly by Longcope (15), and consisted briefly of a history of precordial or substernal pain, frequently nocturnal and associated with paroxysmal dyspnea, clinical or x-ray evidence of changes in the size or contour of the aortic arch, and often a bell-like quality of the second sound at the aortic area.

Aortic regurgitation. As in the preceding group, the incidence of aortic regurgitation is greater in males than in females. In fact, negro males show an incidence more than three times that of negro females, while the difference between white males and white females is not so marked.

Angina. Angina pectoris, presumably on a syphilitic basis, has not been frequent in our clinic, but it is interesting that, despite the high incidence of aortic involvement in negroes, angina has been seen less often in them than in whites. This is true, of course, also in angina pectoris in general, although our dispensary population is not composed of the class of persons considered to be particularly prone to angina pectoris.

Aneurysm. The incidence of aneurysm has approximately the same relative race and sex distribution as does aortic regurgitation, although the actual incidence is lower. The great rarity of aneurysm in females is amply demonstrated, and of our 21 cases all but 3 were negroes. Warthin (16) states that in his autopsy material he has seen an aortic aneurysm in a woman on only two occasions.

The vast majority of the aneurysms in our patients arose from the thoracic aorta, though in a few cases it started from the brachial artery, the innominate artery or abdominal aorta.

Other lesions of the cardiovascular apparatus due to syphilis. Patients with myocarditis, gumma of the heart muscle, disturbances of the conduction system, or other rare lesions, have been placed in this category. In many patients in this group, syphilis, as an etiological factor for a clinical disturbance, has been determined only at autopsy.

Central nervous system. No attempt will be made to cite even the relatively recent literature bearing on the race and sex incidence of syphilis of the central nervous system, as the literature is huge and for the most part the statistics presented are not comparable with ours, in that the former are not compiled on the basis of a known syphilitic population. Then, too, few clinics treating all stages of the disease have employed spinal puncture as a routine diagnostic procedure as generally as we have. Plaut (17) in a recent monograph has given a complete bibliography of the literature on central nervous system syphilis in negroes and Indians.

Although a spinal fluid examination was made in a large majority of all patients admitted to this clinic, it was not obtained in 100 per cent of patients; consequently, some cases of asymptomatic neurosyphilis undoubtedly have been overlooked. Also, a few patients with general paresis have been too disturbed to be managed in the Out-patient Department. With these exceptions, however, the figures

TABLE VIII

Types of central nervous system distributed according to race and sex, with their percentage based on total cases of late syphilis in the respective race and sex group

	WHITE MALES		WHITE FEMALES		COLORED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
General paresis	94	7.1	35	4.5	33	1.9	8	0.3	129	6.1	41	0.9	127	4.2	43	1.2	170	2.7
Tabes dorsalis	139	10.5	23	3.0	42	2.4	15	0.6	162	7.7	57	1.3	181	6.0	38	1.1	219	3.4
Tabes with optic atrophy	31	2.2	7	0.9	14	0.9	1	0.1–	38	1.8	15	0.3	45	1.4	8	0.2	53	0.8
Tabes with charcot joint	16	1.2	6	0.7	4	0.2	1	0.1–	22	1.0	5	0.1	20	0.6	7	0.2	27	0.4
Tabo-paresis	17	1.3	4	0.5	3	0.1	0	0	21	1.0	3	0.1–	20	0.6	4	0.1	24	0.4
Paraplegia	6	0.4	0	0	5	0.2	1	0.1–	6	0.2	6	0.1	11	0.3	1	0.1–	12	0.1
Optic atrophy	31	2.2	4	0.5	14	0.9	1	0.1–	35	1.6	15	0.3	45	1.4	5	0.1	50	0.8
Eighth nerve	11	0.8	5	0.6	31	1.8	11	0.4	16	0.7	42	0.9	42	1.3	16	0.4	58	0.9
Epilepsy	2	0.1	5	0.6	13	0.8	4	0.1	7	0.3	17	0.4	15	0.5	9	0.2	24	0.4
Vascular	18	1.3	3	0.3	42	2.4	15	0.6	21	1.0	57	1.3	60	1.9	18	0.5	78	1.2
Unclassified	154	11.7	82	10.5	171	10.0	126	4.8	236	11.2	297	6.8	325	10.7	208	6.1	533	8.3
Total C. N. S.	519	39.3	174	22.3	372	15.9	183	7.0	693	33.0	555	10.5	891	26.1	357	10.5	1,248	17.8
Total late cases	1,318		780		1,704		2,618		2,098		4,322		3,022		3,398		6,420	

given in Table VIII represent the number and percentage of neurosyphilitics observed in the total syphilitic population of a large general hospital. There is no duplication of patients in this table. The striking difference in the incidence among males and females, on the one hand, and whites and negroes, on the other, seems to be sufficient proof of a profound biological difference in the races and sexes as regards their immunity or susceptibility to changes in the central nervous system due to *Treponema pallidum*. The differences are all the more remarkable in view of the evidence showing that in the early stages of syphilis cytobiological abnormalities in the cerebrospinal fluid are equally frequent in the two sexes (18). In a series of papers (18, 19, 20, 21, 22) from this clinic chiefly by Moore, the material here presented has been discussed in detail from the standpoint of the race and sex differences, and possible explanations for these differences have been advanced. Briefly, those studies deal with two questions, neurotropism and the influence of pregnancy.

The group of neurosyphilitics labelled "C.N.S. unclassified" is composed of a few patients with serious disabling lesions, such as gumma of the brain, involvement of the pituitary, etc., but the great majority of patients in this group are those with asymptomatic neurosyphilis. If one disregards these patients, the incidence of serious disabling types of neurosyphilis in the white male is 27.6 per cent (of total late cases), in the white female, 12 per cent, in the colored male, 5.9 per cent, and in the colored female 2.2 per cent, differences which are even more marked than when the milder grades are included. I have not included in this study the actual number of patients with asymptomatic involvement of the central nervous system, since this is not a usual diagnosis on admission, although the incidence of this complication in our material can be obtained from a recent paper by Moore (23).

When the incidence of the different types of neurosyphilis is studied, the same striking difference in the races and sexes is noted. General paresis, including those patients in whom there is an associated tabes dorsalis, was more than 7 times more frequent in whites than in negroes, and 28 times as frequent in white men as in colored women. The difference between white males and white females was not so great. Tabes was considerably more frequent in whites and the cases

of tabes and spastic paraplegia, when grouped together, showed the following percentages; for white male, 15.6, for white female 5.1, for colored male, 3.8, and for colored female, 0.8. Primary optic atrophy as an isolated manifestation in tabes was one of the rarest lesions in colored females. The figures for all cases of primary optic atrophy are for the white male, 4.4 per cent, for the white female, 1.4 per cent, for the colored male, 1.8 per cent, and for the colored female, 0.1 per cent. Charcot's joint is another complication which was exceedingly rare among colored women. Epileptiform seizures without focal manifestations, occurring in patients with positive spinal fluids, seem to be most frequent in colored males, with white females next in relative frequency. Cerebral vascular syphilis, as manifested by vascular accidents, follows more nearly the incidence of vascular syphilis in general than of cerebrospinal syphilis, in that males, especially colored males, were more often affected. Eighth nerve lesions occurring in late acquired syphilis were considerably more frequent in men than in women.

Latent. In this classification are placed patients who have no clinical evidence of syphilis but who have either a positive blood Wassermann reaction, a history of inadequately treated syphilis, or who have given birth to a known syphilitic baby. No patient with an abnormal spinal fluid due to syphilis is included in this group even though the nervous system involvement is asymptomatic.

Approximately one-third of all patients with syphilis admitted to the clinic may be placed in this group, although when the figures are analysed more closely it is seen that there is a striking preponderance of women over men. As shown in Table VI, 64 per cent of all women with late syphilis show no specific lesions, while only 41 per cent of men are without some clinical manifestation of the disease. In Table IX the cases of latent syphilis are subdivided according to the evidence on which the diagnosis was based. By far the largest group was made up of patients who did not present any clinical evidence of syphilis but had a positive Wassermann reaction. Moderate glandular enlargement did not exclude patients from the class of latent syphilis.

A smaller group of patients were those who gave a fairly definite history of syphilis, but who on admission showed no clinical or laboratory evidence of the disease. The history was usually that of a

TABLE IX

Latent syphilis (incidence based on percentage of total late cases)

	WHITE MALES		WHITE FEMALES		COLORED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Positive Wassermann only	384	29.1	345	44.3	642	37.6	1,585	60.6	729	34.8	2,227	51.5	1,026	33.9	1,930	56.8	2,956	46.1
History. Wassermann negative	148	11.2	37	4.7	66	4.0	49	1.8	185	8.8	115	2.6	214	7.1	86	2.5	300	4.6
Congenitally syphilitic child—Wassermann positive or negative			54	6.9			105	4.0	54	2.5	105	2.5			159	4.7	159	2.4
Total latent	532	40.3	436	55.9	708	41.6	1,739	66.4	968	46.1	2,447	56.6	1,240	41.0	2,175	64.0	3,415	53.1
Total late syphilis	1,318		780		1,704		2,618		2,098		4,322		3,022		3,398		6,420	

TABLE X

Cases of pulmonary tuberculosis and diabetes mellitus in association with syphilis

	WHITE MALES		WHITE FEMALES		COLORED MALES		COLORED FEMALES		WHITE		COLORED		MALES		FEMALES		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Syphilis and pulmonary tuberculosis	42	1.9	19	1.5	40	1.4	42	1.1	61	1.7	82	1.2	82	1.6	61	1.2	143	1.4
Diabetes mellitus	9	0.4	6	0.4	14	0.5	10	0.2	15	0.4	24	0.3	23	0.4	16	0.3	38	0.3
Total syphilitic cases	2,213		1,225		2,804		3,758		3,438		6,562		5,017		4,983		10,000	

diagnosis of syphilis followed by treatment in amounts which we consider usually inadequate to eradicate the infection.

The majority of women who had given birth to a syphilitic baby had a positive Wassermann reaction, although a few had negative Wassermann reactions even though they had received no antisyphilitic treatment. The presence of a syphilitic lesion, of course, excluded patients from this group. Among the latent syphilitics 67 or 15.3 per cent of the white females and 511 or 29.2 per cent of the colored females were pregnant on admission to the clinic. These figures do not include the women who became pregnant after admission to the clinic or those pregnant women who showed some syphilitic lesion at the time of admission.

Syphilis in association with other diseases. The incidence of pulmonary tuberculosis and diabetes in our patients is shown in Table X. The reported incidence of pulmonary tuberculosis in Baltimore in 1928 was for whites, 0.86 per cent, and for negroes, 2.61 per cent, although the incidence among the dispensary class of whites is undoubtedly higher. On the basis of these figures it would seem that syphilis at least does not predispose a patient to pulmonary tuberculosis, and indeed in the case of negroes pulmonary tuberculosis seems to be considerably less frequent in syphilitics than in the general negro population.

Diabetes mellitus was seen no more frequently in patients with syphilis than in patients who are non-syphilitic.

SUMMARY

1. Statistics have been presented bearing on the incidence of various types of syphilitic lesions in each sex and in two races, whites and negroes, in a total of 10,000 ambulatory patients above the age of 12 years known to have syphilis.

2. The total number of cases was approximately equally divided among the three stages of syphilis—early, tertiary, and latent. Of the total cases 3.4 per cent had congenital syphilis.

A. Early syphilis:

3. During the past 10 years there has been observed a steady decline in the number of cases of early syphilis, *i.e.*, of recent infections, in whites, especially white males.

4. Genital chancres were observed but rarely in females. A slightly higher percentage of white males came under observation during the primary stage than did colored males, and a much higher proportion of the former were seen in the sero-negative phase.

5. Reinfection was observed more than 7 times as frequently in males as in females.

6. Acute iritis occurred in 5.5 per cent of patients with secondary syphilis, although it was twice as frequent in negroes as in whites.

7. The incidence of acute meningitis in whites was approximately twice that in negroes, and in males twice that in females.

The incidence of neurorecurrence was higher in whites than in negroes, and higher in males than in females.

B. Late syphilis:

8. Lesions of the skin and mucous membranes occurred with about equal frequency in the two races and the two sexes. The incidence in the total late cases was 8.8 per cent.

9. Lesions of the skeletal system were observed in 8.8 per cent of the total late cases. The incidence for whites was 5.7 per cent and for colored 9.4 per cent, while the incidence in each race was higher in the males.

10. Syphilitic stricture of the rectum was confined almost entirely to colored females.

11. Gumma of the lymph nodes was an uncommon manifestation. It occurred preponderantly in negroes.

12. Clinically recognizable syphilitic affections of the cardiovascular system, excluding cerebral vascular lesions, occurred in 10 per cent of all late cases; the proportion of males to females, and negroes to whites was approximately as 2 to 1.

Uncomplicated aortitis, with or without aneurysm, occurred much more frequently in males than in females and in negroes than in whites. Aortic regurgitation was more than twice as common in males as in females, although it was nearly as common in whites as in negroes.

Syphilitic angina pectoris was rare but was more common in whites and in males, respectively, than in negroes and females.

13. Central nervous system syphilis was observed in late syphilis in 39.3 per cent of white males, in 22.3 per cent of white females, in 15.9 per cent of colored males, and in 7.0 per cent of colored females.

When serious disabling types of central nervous system syphilis only are included, the percentages are for white males 27.6, for white females 12.0, for colored males 5.9, and for colored females 2.2.

General paresis was 7 times as frequent in whites as in negroes, and 28 times as frequent in white men as in colored women.

Tabes dorsalis with or without optic atrophy or Charcot joint was much more common in white males than in white females or negroes of either sex. It was exceedingly rare in negro females.

Cerebral vascular syphilis was observed somewhat more frequently in negroes than in whites.

14. Of the syphilitics observed in the period of latency the proportion of females to males was as 3:2.

15. The incidence of pulmonary tuberculosis among our negro syphilitics was decidedly less than the incidence in the general negro population. The incidence of pulmonary tuberculosis among the general dispensary class of whites was not available.

Diabetes mellitus was no more frequent among syphilitics than among non-syphilitics.

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OCULAR LESIONS IN FETAL SYPHILIS[1]

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A review of the literature reveals an almost complete absence of information concerning the ocular lesions of fetal syphilis. This is most surprising in view of the great interest and the voluminous literature that exist on the one hand concerning fetal syphilis in general, and on the other hand, concerning ocular syphilis in general. The ophthalmoscopic picture of congenital syphilitic chorioretinitis differs in many cases quite fundamentally from that of chorioretinitis, both in acquired syphilis and in non-specific ocular disease. Irido-cyclitis in congenitally syphilitic infants likewise differs from syphilitic iridocyclitis in the adult. It is difficult to understand why these peculiar, and, in their late stages, clinically familiar lesions have not aroused more interest, for material is available for their investigation in every hospital that has a large obstetrical service.

The following study is based upon the routine postmortem examination of the eyes of 175 infants who were either still-born or who died during the first months after birth. The autopsies on these infants were performed by various members of the Department of Pathology. Microscopic sections were made of all the eyes so obtained. In 30 out of the total number of infants in this series the diagnosis of congenital syphilis was established. In 9 of the 30 syphilitic infants ocular inflammatory lesions were found. No such lesions were seen in the non-syphilitic infants.

Before reporting these 9 cases in detail the scanty literature on this subject may be briefly discussed. Spirochaetes have been found in the eyes of syphilitic infants by Bab (1), Schlimpert (2), and Waetzold (3), who have demonstrated their presence in all mesodermal ocular structures. Our own experience is that spirochaetes are not often found in great numbers in these eyes, and that when found they are most frequently present in the sheaths of the blood vessels which per-

[1] Read before the American Ophthalmological Society, June, 1929.

forate the sclera in the region of the ciliary body. Two of these writers state that there was a diffuse mononuclear infiltration of the uvea (iris, choroid and ciliary body) in the cases in which they found spirochaetes. Rumbaur (4) and Yoshida (5) have each reported a case of diffuse mononuclear infiltration in the iris of a congenital syphilitic infant under one month of age. Loktew (6) reports the constant finding of pathological changes in the eyes of ten syphilitic infants (7

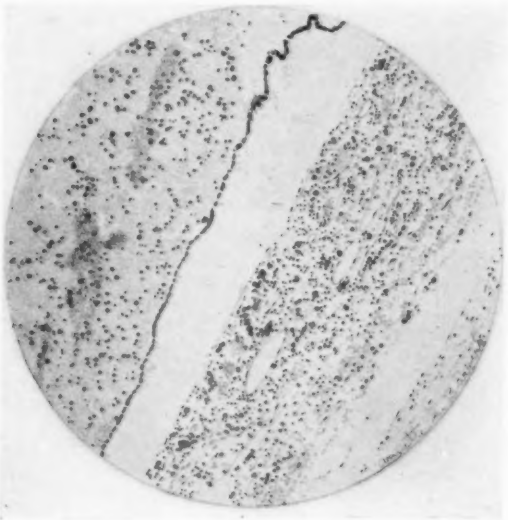

FIG. 1. CASE I. MYELOID INFILTRATE IN THE CHOROID

days to 10 months old): endo- and perivascularitis, hyalin changes in the vessel walls, round cell infiltration of the uvea and optic nerve, and (in 2 cases) of the deeper layers of the retina. Igersheimer (7) has investigated a similar series of cases without finding the lesions described. Rochon-Duvigneaud (8) found in the eye of a two-months old congenital luetic infant a large chorioretinal scar, together with diffuse cellular infiltration of the choroid, especially of the choriocapillaris.

From the clinical side information is equally scanty. The characteristic ophthalmoscopic pictures of congenital lues are, of course, familiar

to every clinician, but these represent the end results of the inflammatory process rather than its active stages. The clinical classification of these ophthalmoscopic pictures has, however, been somewhat confused. It may, therefore, not be out of place to outline the main types, attempting so to arrange them as to make their pathological interpretation clearer.

1. Circumscribed chorioretinitis. These cases show focal lesions, sometimes multiple, in the choroid and retina. They occur at any time in the life of a congenital luetic, ante-, or post-natal, and are not essentially different from similar lesions in acquired syphilis, or in non-specific ocular disease. Their active stages have not heretofore been observed either clinically or pathologically in the fetus or infant. They produce dense, circumscribed scars which reveal themselves ophthalmoscopically as chalky white patches surrounded by heaped up choroidal pigment.

2. Salt and pepper fundus. This ophthalmoscopic picture is characteristic of congenital lues, and since it is often found early in life the presumptive evidence is strong that it is the outcome of fetal or early infantile inflammation. It represents the end result of a lesion, the active stage of which is unknown to the ophthalmoscopist. We shall attempt to show that the early stages of this lesion are characterized by a diffuse infiltration of the choroid with inflammatory cells, the reaction being most intense in the superficial layers of the choroid, namely, the choriocapillaris. Subsequently, a fine diffuse scarring develops, with great disorganization of the choroidal capillary bed. Finally, as has been demonstrated by Staehli (9) and Stock (10), the layer of pigment epithelium and the rods and cones, which are little affected by the inflammatory process, but which depend on this capillary bed for their nutrition, become atrophied and disorganized, the pigment being heaped up at one point, absent at the next. The resulting peppery appearance of the fundus is easily understood.

3. Retinal scarring with atresia of the retinal blood vessels and optic atrophy. This somewhat more rare ophthalmoscopic picture is generally associated with lesions of type (2), and is also to be attributed to an inflammatory process, the active stage of which has occurred early in life. It is characterized by the formation of widespread veils of connective tissue in the retina, together with marked atresia of the

retinal blood vessels, with blurring of the disc margins and a muddy white appearance of the disc.

4. Retinitis pigmentosa. Under this descriptive name are grouped together a medley of cases of widely divergent pathogenesis. The relatively common familial type of this disease has, of course, nothing to do with syphilis. The same may be said of those extremely rare cases which have been found to develop after severe septic infections. The syphilitic cases of retinitis pigmentosa are separable into two groups,—those which develop in infancy and which are merely an

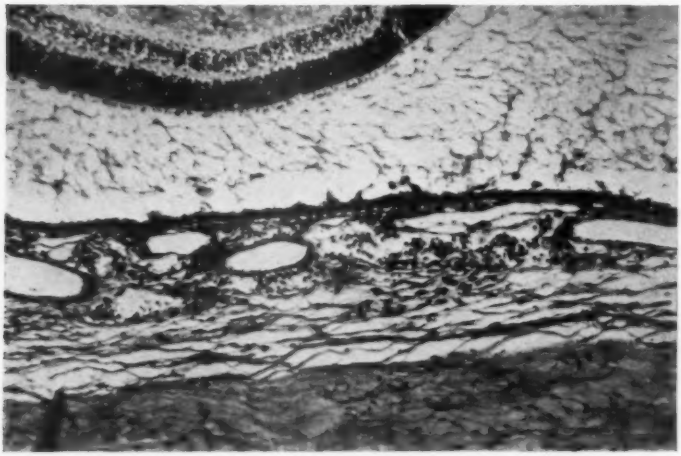

FIG. 2. CASE II. FIBROSIS AND INFILTRATION IN THE CHOROID

exaggeration of the "salt and pepper" process; and those which develop late in life. These latter are perhaps to be related to late central nervous system syphilis with which they are not infrequently associated.

From this brief summary a distinct parallelism between the ocular and the visceral lesions of congenital syphilis can be made out. The characteristic feature of fetal and early infantile lesions is its diffuseness and its resultant fine interstitial scarring. Later on, circumscribed focal lesions—gummata—dominate the picture. Finally.

there is a small group of cases with fine chorio-retinal scarring occurring late in life, which may be related in their pathogenesis to late neuro-syphilis.

In regard to syphilitic irido-cyclitis a similar parallelism can be seen clinically. The characteristic feature of the lesions in the iris and ciliary body in acquired lues is the focal character of the injury associated with marked tissue destruction, violent inflammatory reaction, and dense scarring. In infants, on the other hand, the inflammation is diffuse, relatively mild, and, unless glaucoma occurs as a complication, little distortion of the tissues or obvious scarring is seen; while in late neuro-syphilis, in association with the loss of pupillary reaction, an atrophy and perhaps also a fine interstitial scarring of the iris occurs.

REPORT OF CASES

Case I. Johns Hopkins Hospital Autopsy No. 8710. Colored male infant.

Clinical history. Premature, died 3 hours after birth, maternal Wassermann positive.

General anatomical findings. Autopsy performed by Dr. Kindell. Lymph glands and spleen enlarged. Hemorrhages in the meninges. Blood formation in liver and kidneys. Fibrosis and cellular infiltration in the pancreas. Perivascular infiltrates in kidneys. Thickened alveolar walls and slight mononuclear infiltration in the lungs. Characteristic syphilitic osteochondritis. Spirochaetes found in the adrenal, intestinal wall and pancreas.

Ocular findings. Only one eyeball was obtained for study. This was fixed in Bouin solution and imbedded in paraffin. Sections were stained with haematoxylin and eosin and with Wright's blood stain.

The anterior segment of the eyeball is normal. There is a small retrobulbar hemorrhage which was evidently an antemortem occurrence, since it contains phagocytic cells filled with blood pigment. The choroid contains several scattered areas of myeloid cell infiltration. The largest of these is disc-shaped, measures about 3 mm. in its greatest diameter and is capped by a subretinal hemorrhage. There is a rather extensive hemorrhage into the stroma of the choroid. This, together with the cellular infiltrate, causes a considerable thickening of the choroid which at a maximum reaches about three times the normal dimension. The infiltrate is very loosely arranged. In the center of the largest lesion it occupies the whole thickness of the choroid, toward the edges, and in the small foci only the anterior layers of the choroid are involved. In spite of hemorrhage and infiltration the structure of the choroid is little damaged.

On account of the looseness of the choroidal stroma the cells involved in the infiltrate can very readily be studied. All types of bone marrow cells are seen,—

myelocytes, myeloblasts, a few polymorphonuclear leucocytes, nucleated red blood cells and megalokaryocytes,—together with a small number of lymphocytes. The retina, outside of a localized detachment due to subretinal hemorrhage, is normal. The optic nerve shows no lesion.

Case II. Johns Hopkins Hospital Autopsy No. 7824. White male infant.

Clinical history. Father and mother have negative blood Wassermann reactions, but the father has had an incomplete course of antiluetic treatments. The mother has had three pregnancies, the last two were premature The last child,

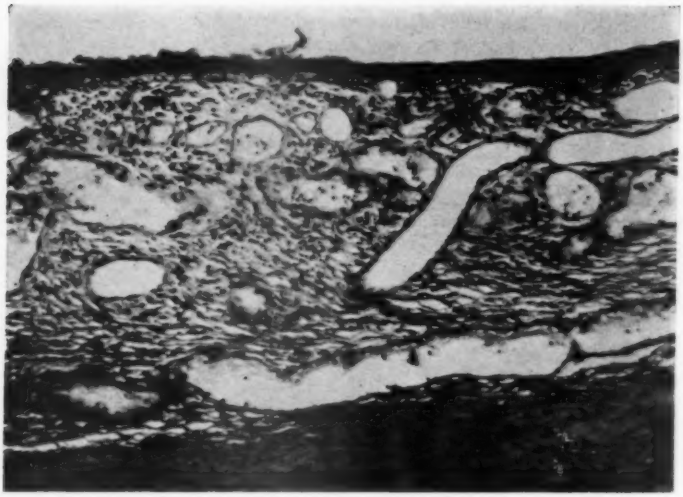

FIG. 3. CASE II. FIBROSIS OF THE CHOROID

the one which we are reporting, was 2 to 3 months premature. At the age of two weeks there was a vesicular eruption on the arms which soon disappeared. The infant was jaundiced from birth. At the age of two months,—eleven days before death,—it developd a cold and cough, began to vomit and to have frequent loose stools.

Examination at the Harriet Lane Home, to which the child was admitted, revealed jaundice, enlarged liver and spleen, bilateral otitis media. There was fever, W.B.C. 15,000, bile in the urine. The child developed a bronchopneumonia and died a few days after its admission to the hospital. Wassermann not done.

Clinical impression. Prematurity, otitis media, Icterus neonatorum, Acute gastrointestinal indigestion, Terminal bronchopneumonia.

General anatomical findings. Autopsy performed by Dr. Seidlin. The body was 48 cm. long, weighed 2.6 kgm. There was marked jaundice. Liver, spleen and lymph glands were enlarged. Microscopic study of the organs revealed the following:

Liver: Bile-stained, fatty degeneration, diffuse scarring, numerous areas of blood formation,—mostly neutrophilic myelocytes.

Kidneys: Islands of blood formation, perivascular myeloid infiltration, no neogenic zone.

Lungs: Confluent bronchopneumonia,—polymorphonuclear leucocytes and giant cells in the alveoli, myeloid cells in the bronchial walls.

Bones: Slight fibrosis of the shafts, irregular line of ossification, hyperplasia of the marrow.

Testes: Diffuse scarring, atrophy of the tubules, myeloid infiltration.

Intestine: Myeloid infiltration in the submucosa.

No spirochaetes were found in spite of careful search.

General anatomical diagnosis. Congenital syphilis, bronchopneumonia.

Ocular findings. Only the posterior segments of the eyes were obtained for study. Fixation, etc., as in previous case. Serous detachment of both retinae, in one eye complete, in the other only partial.

On section the most intense lesion is seen in the anterior layers of the retina, which are swollen, and diffusely infiltrated with mononuclear, mostly myeloid cells. In some places, especially near the optic disc, there is an extraordinary development of young granulation tissue replacing the anterior layers of the retina and separated from the deeper layers by large spaces containing serum. Scattered wandering cells are found over the surface of the retina and also in the serous fluid that separates it from the choroid. At one place there is a small chorioretinal adhesion, with complete disorganization of the retina and of the choriocapillaris, and their replacement by granulation tissue in which are scattered pigment-bearing cells, probably derived from the pigment epithelium.

There is a diffuse fibrosis of the choroid, more marked in one eye than in the other, with extensive infiltration, both focal and diffuse, with myeloid and mononuclear cells. The infiltration is most marked in the choriocapillaris.

The optic nerve shows an extreme degree of disorganization. The nerve fiber bundles cannot be recognized. They have been replaced by an overgrowth of very cellular glial and connective tissue, which is densely infiltrated with myeloid cells. There is a slight cellular infiltrate in the meninges of the optic nerve. Slight perivascular infiltrate about some of the posterior ciliary vessels.

Case III. Johns Hopkins Hospital Autopsy No. 7969. Colored male infant.

Clinical history. Premature; died 4 hours after birth; maternal Wassermann positive.

General anatomical findings. Autopsy performed by Dr. Riehl. Typical syphilitic lesions in lungs, liver, pancreas, kidneys and bones. Extremely widespread blood formation.

Ocular findings. The histological picture in this case is somewhat blurred by postmortem changes. One eye showed no lesions. In the anterior part of the choroid of the other eye there was a large area of hemorrhage and infiltration. In spite of the postmortem changes some of the infiltrating cells are still recognizable as myelocytes. One small chorioretinal scar like that seen in Case II was found at the posterior pole. The ganglion cells of the retina have completely disappeared and in the neighborhood of the optic disc a slight round cell infiltration of the anterior layers of the retina can be made out, together with a slight growth of newformed capillaries. The optic nerve is greatly disorganized, its fiber columns are

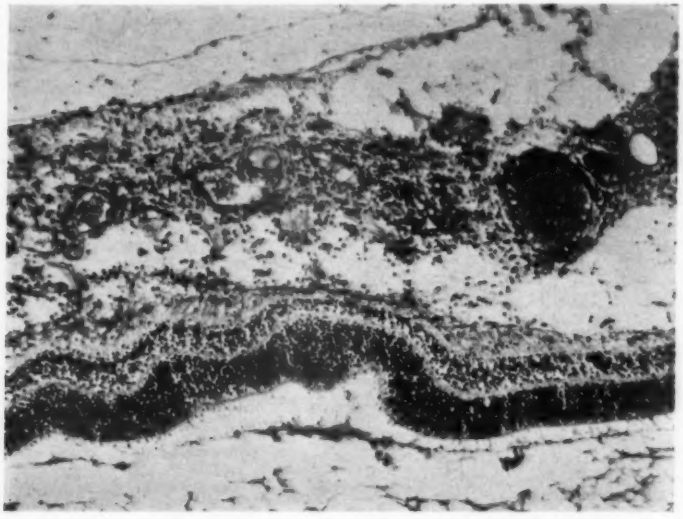

FIG. 4. CASE II. RETINAL LESION

no longer recognizable and are completely replaced by a very vascular tissue. In the cornea there is a peculiar circumscribed nodule of organizing cellular infiltration. Otherwise the anterior segment of the eye is normal.

Case IV. Johns Hopkins Hospital Autopsy No. 10084. Colored infant.

Clinical history. Full term infant; maternal Wassermann positive; the child cried only after prolonged stimulation; died one and a half days after birth.

General anatomical findings. Autopsy performed by Dr. Bumstead. Findings negative except for eyes.

Ocular findings. One eye is normal. In the choroid of the other eye there is an extensive area of cellular infiltration accompanied by hemorrhage. The in-

filtrating cells are mainly lymphocytes. No myeloid cells are seen. Elsewhere in this eye the choroid seems somewhat more cellular than normal, though no lesions can be made out.

The cases so far reported illustrate varying degrees and stages of a chorio-retinal inflammatory disease, which, in view of its histological picture and of the associated findings is undoubtedly syphilitic in origin. In the next two cases a mild choroidal reaction of the same type is combined with a lesion of the iris and ciliary body, the latter, however, so slight and so lacking in any characteristic syphilitic features that, but for the associated lesions, one would not be inclined to

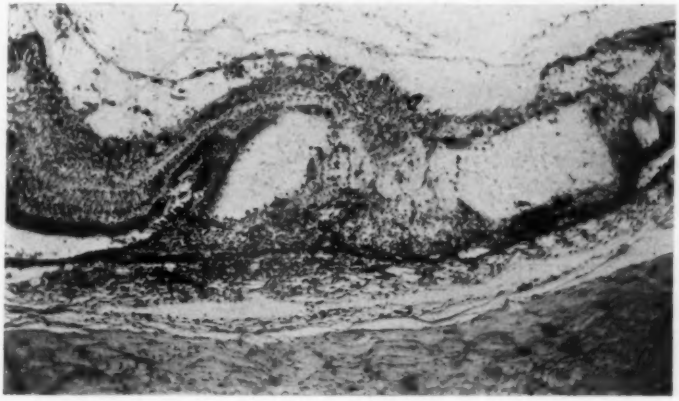

FIG. 5. CASE II. LOCALIZED CHORIORETINITIS

regard it as syphilitic. In Case V, however, no other possible cause for the iritis can be advanced. We are thus able to bridge over the gap to these mild cases of irido-cyclitis, which, as will be seen, are not uncommon in fetal syphilis, and which, in their more severe forms, are recognizably syphilitic in character.

Case V. Johns Hopkins Hospital Autopsy No. 9204. Stillborn, colored infant.

Clinical history. Mother has two term children living, followed by three still births, including this infant, all 7 months premature. Maternal Wassermann positive. The infant at birth gave one or two gasps and died.

General anatomical findings. Autopsy performed by Dr. MacDonald. Extreme syphilitic lesions in practically all organs. Spirochetes present.

Ocular findings. There are scattered small foci of myeloid cell infiltration in the choroid in each eye, mainly in the choriocapillaris. The general configuration of the lesion is identical with those already reported. In addition there are a small number of mononuclear wandering cells scattered over the surface of the iris and in the iris stroma. Retina and optic nerve are normal.

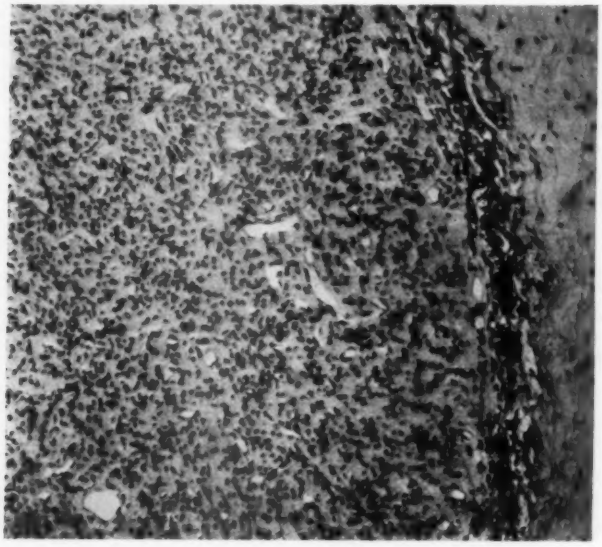

FIG. 6. CASE II. OPTIC NEURITIS

Case VI. Johns Hopkins Hospital Autopsy No. 10315. Age 3 months, colored male infant. Autopsy performed by Dr. Kindall.

Clinical history. Father 28, whereabouts unknown. Mother 23, living and well, no history of syphilis or tuberculosis, no other pregnancies. Present infant premature, did poorly, brought to the hospital on account of fracture of the right humerus. Examination revealed a hemorrhagic discharge from the nose, swelling and crepitus about the head of the humerus, cutaneous lesions on face and scrotum, Wassermann positive. *Clinical impression:* Congenital syphilis, fracture of the head of the humerus.

General anatomical findings. Osteomyelitis of humerus and ulna; purulent meningitis (pneumococcus); extreme syphilitic changes in the bones; typical syphilitic lesions in the skin and intestine; spirochetes demonstrated.

Ocular findings. In one eye the cornea is normal. There is a deposit of mononuclear cells, mainly lymphocytes, on the surface of the iris and at the angle of the anterior chamber. There is a slight infiltration of the iris stroma with the same cells, more intense in the superficial layers. A similar diffuse cellular infiltrate is to be found in the ciliary body. The choroid shows only a very slight infiltration except in one small area near the equator where a moderate accumulation of lymphocytes is found. The retina and optic nerve are normal, but the meninges of the nerve are intensely infiltrated with polymorphonuclear and mononuclear cells. The other eye shows essentially the same picture except that the choroidal infiltration is absent.

Case VII. Johns Hopkins Hospital Autopsy No. 10540. Age 4 weeks, white female infant. Autopsy performed by Dr. Kindall.

Clinical history. Maternal Wassermann positive. Mother has had one miscarriage and also twins who died in infancy of mastoiditis. This infant, born prematurely, had icterus neonatorum, developed acute nephritis and diarrhoea, and died at the age of 4 weeks.

General anatomical findings. Typical syphilitic lesions are present in the bones, lung, liver, spleen, intestine and kidneys. Spirochetes were found in large numbers in the bones, lung, and intestinal wall.

Ocular findings. Both eyes show similar conditions. In each the choroid and retina are normal. The anterior chamber contains an inflammatory exudate of serum, fibrin, and mononuclear cells. Over the surface of the iris, at the angle of the anterior chamber and on the pupillary membrane, which persists in its fetal vascularity, is a heavy deposit of large mononuclear wandering cells. The iris is thickened, more fibrous than normal, and infiltrated with the same cells. The pigment epithelium of the iris and ciliary body is separated from the stroma by a similar inflammatory exudate and some new-formed granulation tissue. In the ciliary body there is an infiltrate both diffuse and focal, in part distributed about blood vessels. The ciliary body is much disorganized in its finer structure. The ciliary muscle has been largely destroyed and is replaced by fine, irregularly arranged scar tissue. Most of the inflammatory cells are lymphocytes and large mononuclear phagocytes, but occasional myelocytes can be found. One eye was stained by the Levaditi method. Spirochetes can be seen in large numbers in the iris and ciliary body, especially in the walls of the blood vessels.

Case VIII. Johns Hopkins Hospital Autopsy No. 10709. White female infant, aged 6 months. Autopsy by Dr. Forbus.

Clinical history. Maternal Wassermann and family history not reported. The infant was born prematurely. After various nutritional difficulties it developed diarrhoea, marasmus, and finally otitis media complicated by acute nephritis. Wassermann reaction positive. At the age of 6 months, in a marantic condition. the infant died.

General anatomical findings. In the organs no syphilitic lesions were found, the only abnormalities being otitis media, emaciation, and mild subacute nephritis.

Ocular findings. The tissues are much autolized. In each eye there is a deposit of mononuclear cells over the surface of the iris with a slight infiltration of the iris stroma, most marked near the anterior surface. At the iris root, and in the angle of the anterior chamber, the cellular accumulation is more intense. The ciliary body, choroid, and retina show no lesions.

Case IX. Johns Hopkins Hospital Autopsy No. 9600. Premature, still born infant. Autopsy performed by Dr. Goode.

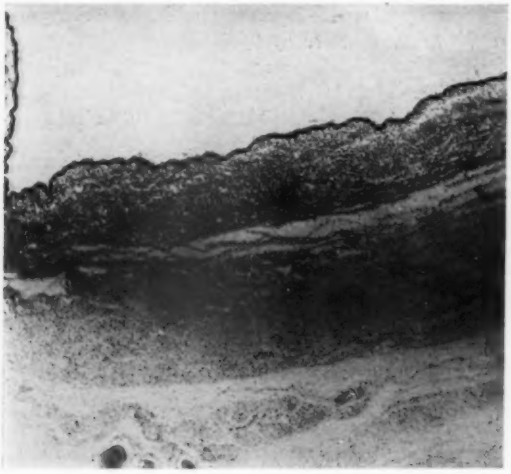

FIG. 7. CASE III. HEMORRHAGE AND INFILTRATE IN THE CHOROID

Clinical history. Maternal Wassermann not reported. Father has a generalized rash. No previous pregnancies. Infant born prematurely at 7 months.

General anatomical findings. Retardation in development of the pancreas, kidneys, and lungs, with myeloid infiltration in the kidneys and pancreas. No spirochetes were found. On the basis of the anatomical findings the diagnosis of congenital syphilis was considered very probable.

Ocular findings. The eyes show persistent pupillary membranes, a small nodule of cartilage in the sclera, and other signs of incomplete development. There is a slight mononuclear infiltrate over the surface of the iris with slight infiltration of the anterior stroma. There is no distortion or scarring of the iris stroma, and the other intraocular structures show no lesions.

DISCUSSION

In the interpretation of these cases several problems arise: (*a*) as to the syphilitic nature of the lesions; (*b*) as to the significance of the myeloid cells found in the lesions of a number of the cases; (*c*) as to the clinical interpretation of the histological findings.

a. The high frequency of the lesions which we have described in cases of congenital syphilis, together with the absence of similar lesions in a much larger group of non-syphilitic infants, speaks strongly for

FIG. 8. CASE III. LOCALIZED CHORIORETINITIS

the syphilitic origin of the reaction. Among 145 infants in the control series only one showed a mild diffuse infiltration of the choroid and iris, similar to that seen in Case V above. In this case, Johns Hopkins Hospital Autopsy No. 9616, no clinical or anatomical findings are reported which would support the diagnosis of congenital syphilis, but the Wassermann reaction was also not reported in this case and syphilis cannot be excluded. We feel justified, therefore, in omitting this case from further consideration.

In regard to the choroidal and retinal lesions in Cases I to VI, the myeloid character of the infiltrate, the diffuse scarring, the growth of

granulation tissue in the more active lesions, all are closely in accord with the anatomical findings in fetal syphilis in other organs. Furthermore, as will be shown below, it is possible to correlate these findings with various aspects of the familiar ophthalmoscopic picture of congenital syphilis in its later stages. We can conclude, therefore, with a high degree of certainty that these lesions are syphilitic.

In the anterior uveal inflammations which we have reported myeloid cells could be found only after prolonged search, and in the milder instances, Cases V, VI, VIII, and IX, nothing characteristically syphilitic could be discovered in the lesion; but two of these, Cases V and VI, occurred in eyes with typical choroidal lesions. Finally Case VII, which represents a severe form of irido-cyclitis, presents an histological picture which is, in itself, strongly suggestive of syphilis, and in this case spirochetes were found in abundance in the iris.

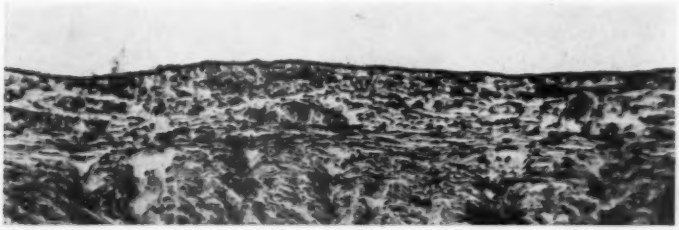

FIG. 9. CASE V. MILD CHOROIDAL LESION

b. The frequent predominance of myeloid cells in the ocular lesions of fetal syphilis is thoroughly in accord with the findings in other organs in the same condition. In regard to the latter a prolonged discussion is to be found in the literature. One school of writers point out that in the embryo the whole mesoderm is actively engaged in blood formation, that in the normal fetus islands of blood formation in the liver and spleen are regularly found, and that it is only in the first weeks after birth that the final predominance of the bone marrow is definitely established even in the normal infant. They regard the myeloid infiltrates in syphilitic fetuses, therefore, as essentially islands of persistent blood formation, and as evidence of a delayed maturation of the blood-forming organs, but not as active participants in an in-

flammatory reaction. The adherents of the second school admit the delayed maturing of the blood forming organs in the syphilitic fetus, and accept as islands of persistent blood formation the myeloid infiltrates so commonly found in the liver and spleen. But the perivascular infiltrates in the kidneys, the lesions in the lungs, intestines, and other organs, which are associated with a growth of granulation tissue and subsequent scarring, bear such convincing evidence of tissue damage as to vitiate the notion that these lesions also are merely

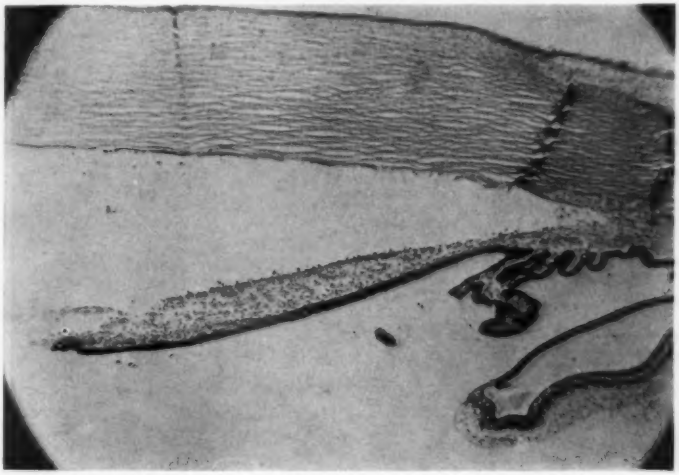

FIG. 10. CASE V. MILD DIFFUSE INFILTRATE IN THE IRIS

islands of blood formation. These writers believe, therefore, that, in the immaturity of the blood-forming organs in fetal syphilis, only a small number of mature wandering cells are available to respond in an inflammatory reaction, and that the deficit is made up by an outpouring of immature myeloid cells.

The presence of myeloid cells in the lesions of the retina and optic nerve in Cases II and III seems to us conclusive evidence in favor of this second hypothesis. At no time in fetal life can active blood formation be found in the retina or optic nerve in the normal embryo or fetus.

c. In attempting to correlate our findings in the choroid and retina with the well known ophthalmoscopic pictures of the later stages of this disease we shall revert to the classification outlined above.

1. Circumscribed chorio-retinal scars. The early stages of these lesions are clearly shown in Cases II and III. Here we have, along with a variety of other findings, localized areas, 0.5 to 1 mm. in diameter, in which the superficial layers of the choroid and the overlying retina are completely destroyed and replaced by a growth of granulation tissue with intense inflammatory infiltration.

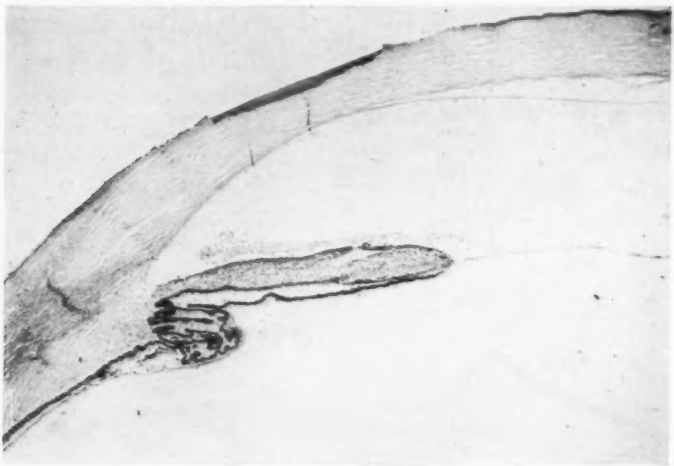

FIG. 11. CASE VII. SEVERE IRIDOCYCLITIS

2. The salt and pepper fundus. The understanding of this characteristic ophthalmoscopic picture has been greatly advanced by the studies of Staehli (9) and Stock (10), who have demonstrated in the later stages of this condition a diffuse fibrosis of the choroid, especially of the chorio-capillaris, and have shown that the death of the rods and cones, and the irregular migration of the pigment epithelium is a result of the disappearance of the choroidal capillary layer. Ito (11) reports on a $2\frac{1}{2}$-year-old child in which the choroid was in great measure replaced by granulation tissue, the chorio-capillaris was completely

destroyed, slight diffuse and occasional focal lymphocytic infiltration was found throughout the choroid, with extensive destruction of the pigment epithelium, scarring and infiltration especially of the anterior layers of the retina. Case II illustrates essentially the same condition at a much earlier age, while Cases I, III, IV, V, and VI show, in varying degrees of intensity and extent, the inflammatory reaction which must be antecedent to such scarring.

3. Retinal scarring with atresia of the retinal blood vessels and optic atrophy. As just noted Ito (11) has described the active stage of this lesion in a child aged 2½ years. Cases II and III reveal the same condition in earliest infancy and in the fetus. Not only are the anterior layers of the retina destroyed and replaced by granulation tissue, but a similar process is seen in the optic nerve.

Inflammatory lesions of the iris and ciliary body occur in this series in much high frequency than they have, heretofore, been noted in living children. In four of the five cases, however, the lesion is so slight that, in all probability, it would have escaped clinical notice. Perhaps more careful clinical observation of syphilitic infants in the early months of life might reveal a higher frequency of these mild cases. The one severe case, one out of thirty cases of congenital syphilis, is hardly unexpected, especially when one considers that the syphilitic infection was unusually severe in this group of cases, so severe, in fact, as to have been the cause of death, or a major contributing factor, in the large majority of these cases.

SUMMARY

Nine instances of intraocular inflammatory lesions in syphilitic infants are described.

The lesions are in accord both with those of fetal syphilis in other organs, and with the clinical and pathological findings in the ocular lesions at a later stage.

On the basis of this pathological analysis a new clinical classification of the ophthalmoscopic pictures of congenital syphilis is given.

The part played by myeloid cells in the lesions of fetal syphilis is discussed.

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THE CARDIAC OUTPUT IN HYPERTHYROIDISM[1]

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The estimation of the cardiac output, especially because of its bearing upon the work of the heart, is of importance in the study of disease. It has long appeared probable that the principle proposed by Zuntz (1), and more particularly by Krogh and Lindhard (2, 3, 4), would prove satisfactory and reliable. This consists in measuring the rate of absorption of an inert gas (nitrous oxide) from the alveolar air into the blood, where its absorption coefficient is known. Their original method, however, has not proven very satisfactory for use upon untrained subjects, and the attainment of complete gas mixture in the lungs, during the time allotted for it in the determination, has been questioned from various sources. The important simplifications recently introduced by Marshall and Grollman (5), and by Grollman (6), and particularly their careful study of the question of gas mixture in the lungs during the experimental procedure, appear to have solved those difficulties.

Of the different conditions which may be expected to produce variations in the cardiac output at rest, alteration in the metabolism is evidently of primary importance. In this paper we are concerned with the cardiac output in hyperthyroidism, in which the basal metabolism is characteristically elevated.

Measurements of the output of the heart in hyperthyroidism were made by Plesch (7) in 1909. Standard basal conditions do not appear to have been maintained in these studies. He reported, using a modification of the Fick method, that with an increase of the basal metabolism of 61 per cent the cardiac output increased but 21 per cent. He considered, therefore, that the utilization of oxygen in the blood was more complete in this disease.

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[2] Jacques Loeb Fellow in Medicine.

Davies, Meakins and Sand (8) reported observations upon fifteen cases of hyperthyroidism (two with toxic adenomata), and in six of these cases observations were made before and after operation. They found, in general, that the increase of metabolism coincided with the increase in cardiac output per minute, but a complete parallelism could not be traced. A particularly high oxygen saturation (85 per cent or more) of the venous blood from the median basilic vein was found, confirming, in their opinion, this increase in blood flow. Thus they believe, contrary to Plesch, that the evidence favors a very low oxygen utilization in hyperthyroidism. Their determinations were not made under basal conditions, since "it was impossible to carry out the numerous and consecutive observations necessary and at the same time maintain the patients under basal conditions." All recent work, however, has indicated the necessity for maintaining standard basal conditions as well as the importance of attention to posture in blood-flow studies.

Liljestrand and Stenström (9) have made a recent contribution to this problem, using the Krogh-Lindhard method with the simplifications introduced later by Lindhard. They studied eleven patients, eight males and three females. All showed an increased cardiac output. In two of the cases, observations were made both before and after thyroidectomy and in both a diminution in blood flow followed operation. Unfortunately, oxygen consumption determinations were not made constantly with each experiment, although standard conditions were rigorously maintained. Wide differences were observed in the results obtained even on the same day and the material was averaged for the expression of their final conclusions. Their female subjects showed an "average" increase of 80 per cent and their male subjects an increase of 100 per cent in the blood flow above the "normal." No really constant relation between cardiac output and metabolism was discernible.

One must conclude that in none of these studies, either because of technical difficulties or because standard conditions were not maintained, was it possible to determine whether a relationship existed between the rate of basal metabolism and the output of the heart measured under basal conditions.

The same difficulty applies to the determinations reported by Robinson (12) on a single patient before and after operation. Previous to thyroidectomy the minute volume was 10,000 cc. and the basal metabolism +58, while after operation the figures found were 4890 cc. and +1, respectively. The cardiac output thus seemed to be increased relatively more than the metabolism. One must feel that the various complicated manipulations—including arterial puncture—required for estimations by the method of Robinson and Burwell, would render its use inadvisable for accurate work with nervous hyperthyroid patients, especially so far as comparisons of blood flow and basal metabolism are concerned. The study of the single case of uncomplicated thyrotoxicosis reported by Burwell and his associates (13) led them to conclude that pulse rate, basal metabolic rate and cardiac output varied together.

The present studies have been made upon eight carefully selected patients, with typical manifestations of the disease, including an elevated basal metabolism, but without evidence of organic cardiac disease or of lung disease either before or after treatment. The clinical examination was confirmed by electrocardiographic studies and x-ray examinations of the chest. The subjects were all co-operative persons of some intelligence. The technique and apparatus were those employed by Marshall and Grollman. The gas used was nitrous oxide. We did not use acetylene because we feared the possible psychic effect of its somewhat disagreeable taste upon patients of this type, and we laid stress upon the importance of making the determination under strictly "basal" conditions, carefully avoiding anything whch would upset mental calm. The effect of loud noises, cold, etc., upon normal persons has been stressed by Liljestrand and others (10). All of the studies were made at least fifteen hours after a light supper, with the patient in the semi-reclining posture (adjustable deck-chair), and after an hour of complete rest. The exclusion of disturbing noise and unusual movement was assured by performing the experiments in a special room set aside for this sole purpose. Our routine was standardized and constantly carried out in the same manner, always by the same worker, in whom the patients gained confidence. This procedure follows: A determination of the oxygen consumption by means of the Krogh basal metabolism apparatus was followed by the

determination of the cardiac output. Finally, a second determination of the oxygen consumption was made, which in all accepted experiments closely checked the first. Cardiac output determinations were made in duplicate by using three evacuated sampling tubes instead of two. Two of these tubes were arranged on capillary tubing (Krogh and Lindhard), connected to one of the side sampling taps. The third sampling tube was connected to the other tap. The sample in tube 1 was taken at the moment of mixing, and samples 2 and 3 at later intervals up to 27 or 28 seconds. The cardiac output could then be calculated by the method given by Lindhard, from samples 1 and 2, and from samples 1 and 3. It should be theoretically possible to calculate the output of the heart from samples 2 and 3 as well, but this is not practical with nitrous oxide. Owing to its greater speed of diffusion and the possibility of more precise gas analysis, this may be done in the case of acetylene.

The determinations were done upon the patients as soon as possible after admission to the hospital, and then at intervals during the course of their treatment, which consisted in rest in bed, a high caloric diet, the administration of Lugol's solution, and finally, subtotal thyroidectomy. The data are collected in Table I.

The first point to be noted is that under these conditions, where quiet and relaxation were realized as far as possible, the increased pulse pressure, usually reported in hyperthyroidism, was not found. Surprisingly little difference, also, was found in the blood pressure before and after treatment, even over prolonged periods. This differs from the view put forward in certain current textbooks. For example, a recent view (11) is as follows: "With younger patients increased pulse pressure is the rule. This increase is not due so much to elevation of systolic pressure as to fall in diastolic—there is often a collapsing quality to the pulse as in aortic insufficiency. In patients over forty the systolic pressure is also often abnormal." The discrepancy is due to the fact that physical and mental rest were more nearly attained under the basal conditions in which our patients were studied. The drop in the diastolic pressure, so often observed and recorded, is usually in proportion to the degree of mental excitement which the patient undergoes as a result of the medical examination. This is clearly indicated in the present patients when the blood pressures

TABLE I

The cardiac out-put per minute in patients with hyperthyroidism

Comparison with the basal metabolism

DATE	WEIGHT	PULSE RATE	BLOOD PRESSURE	BASAL METABOLIC RATE (PERCENTAGE OF NORMAL)	OXYGEN CONSUMPTION	CARDIAC OUTPUT PER MINUTE	OUTPUT PER BEAT	ARTERIAL-VENOUS DIFFERENCE	CARDIAC OUTPUT PER SQUARE METER	REMARKS
Case I. Harrison T. Unit No. 23662. Aged 60, male, height 164 cm.										
1929	kgm.				cc. per minute	liters	cc.	cc. oxygen		
March 23	54.1	111	114/70	+60	331	5.0	45	66	3.13	Lugol's solution 3 cc. daily given from March 19 to April 27
						4.9	44			
March 27	54.7	87	110/74	+19	237	4.5	52	54	2.82	
						4.4	51			
April 6	58.2	86	114/80	+38	283	4.8	56	60	2.86	Operation, April 27
						4.6	53			
May 12	61.7	87	114/78	−1	208	3.0	35	67	1.83	
						3.2	37			
May 22	62.3	86	114/78	+6	229	3.4	39	67	2.01	
Case II. Otto K. Unit No. 22093. Aged 39, male, height 164 cm.										
1928										
December 8	58	106	114/78	+105	445	7.5	71	59	4.57	Lugol's solution, 3 cc. daily, given from December 7 to December 23
December 12	56	83	116/70	+42	303	6.0	72	50	3.72	
December 15	56.8	72	126/72	+54	343	6.7	93	50	4.25	
						7.0	97			
December 18	57	73	112/62	+31	290	5.9	81	48	3.72	
						6.1	84			Operation, December 23
1929										
January 30	64.3	62	118/75	−7	218	5.1	82	44	2.90	
						4.8	77			
March 2	65	58	114/78	−14	202	4.7	81	42	2.79	
						4.9	84			
May 4	69.1	57	118/78	−9	218	3.4	60	61	2.02	
						3.7	64			
May 25	66.6	54	104/68	−9	216	2.7	50	81	1.57	
						2.7	50			

TABLE I—*Continued*

DATE	WEIGHT	PULSE RATE	BLOOD PRESSURE	BASAL METABOLIC RATE (PERCENTAGE OF NORMAL)	OXYGEN CONSUMPTION	CARDIAC OUTPUT PER MINUTE	OUTPUT PER BEAT	ARTERIAL-VENOUS DIFFERENCE	CARDIAC OUTPUT PER SQUARE METER	REMARKS
Case III. Helen H. Unit No. 22888. Aged 30, female, height 157 cm.										
1929	kgm.				cc. per minute	liters	cc.	cc. oxygen		
February 12	81	86	120/68	+25	292	5.6	65	52	3.07	Lugol's solution 3 cc. daily given from February 13 to February 18
						5.7	66			
February 15	81.3	87	124/72	+20	280	5.8	67	49	3.20	
						6.0	69			
February 18	81.3	87	118/72	+18	277	5.3	61	52	2.88	
						5.3	61			Operation, February 19
						5.3	60			
						5.6	65			
February 27	81.7	82	118/78	±0	233	3.4	42	68	1.84	
						3.4	42			
March 3	80.9	74	114/76	−6	220	3.5	47	65	1.84	
						3.3	45			
March 5	81.7	72	112/74	−8	215	3.6	50	60	1.96	
May 1	93.1	65	116/88	−12	197	3.5	53	57	1.80	
Case IV. Edwin S. Unit No. 23750. Aged 39, male, height 166 cm.										
1929										
March 26	59.3	76	132/82	+37	314	5.8	76	53	3.55	Lugol's solution, 3 cc. daily, given from March 31 to April 10
						6.0	78			
March 27	59.3	71	124/80	+33	305	5.6	79	55	3.34	
						5.5	78			
April 4	61.3	66	118/76	+28	298	4.5	68	66	2.71	
						4.6	69			Operation, April 11, 1929
April 20	63.2	66	118/82	−19	188	2.8	42	72	1.53	
						2.4	37			
April 21	63.5	58	122/82	−21	188	2.8	48	66	1.67	
						2.9	50			
April 25	64.5	66	122/88	−8	217	3.4	52	64	1.98	
						3.4	51			
June 7	66.1	63	118/80	−7	222	3.0	47	74	1.73	
						3.0				

TABLE I—*Continued*

DATE	WEIGHT	PULSE RATE	BLOOD PRESSURE	BASAL METABOLIC RATE (PERCENTAGE OF NORMAL)	OXYGEN CONSUMPTION	CARDIAC OUTPUT PER MINUTE	OUTPUT PER BEAT	ARTERIAL-VENOUS DIFFERENCE	CARDIAC OUTPUT PER SQUARE METER	REMARKS
Case V. Anna K. Unit No. 21808. Aged 54, female, height 167 cm.										
1928	kgm.				cc. per minute	liters	cc.	cc. oxygen		
November 23	60.5	94	150/82	+33	258	4.2	45	62	2.5	Lugol's solution 3 cc. daily given from November 24 to December 4
November 26	59.3	90	148/90	+39	268	5.6	61	48	3.35	
December 4	61.3	90	144/80	+49	290	6.4	72	54	3.78	Operation December 5. Died December 6
Case VI. Anne W. Unit No. 21872. Aged 44, female, height 155 cm.										
1928										
December 7	49.9	92	140/80	+50	275	5.1	57	54	3.47	Lugol's solution 3 cc. daily given from November 28 to December 25
December 11	50.8	96	136/80	+38	260	5.5	58	47	3.72	
December 17	52.1	93	132/76	+45	274	4.9	53	57	3.22	
						4.7	51			Operation, December 26
1929										
January 7	50.2	88	140/84	+21	224	3.9	45	58	2.65	
January 9	50.2	86	136/82	+11	205	3.7	43	55	2.51	
Case VII. Viola J. Unit No. 22870. Aged 25, female, height 149 cm.										
1929										
February 5	45.5	95	124/68	+34	242	5.1	54	48	3.69	Lugol's solution 3 cc. daily given from February 5 to February 17
						5.0	52			
February 13	45.9	90	118/74	+26	226	4.6	51	49	3.34	
February 16	45.5	88	118/76	+27	229	4.6	52	50	3.36	
										Operation, February 18
February 27	45.5	86	112/78	+6	188.5	3.3	39	58	2.37	
						3.2	37			
March 1	46.3	88	114/78	+6	188.8	3.4	39	55	2.50	
						3.5	40			
March 5	46.3	83	114/80	+4	184	3.4	41	54	2.46	
April 15	46.3	72	110/78	−3	174	3.3	46	52	2.46	
						3.5	48			

TABLE I—*Concluded*

DATE	WEIGHT	PULSE RATE	BLOOD PRESSURE	BASAL METABOLIC RATE (PERCENTAGE OF NORMAL)	OXYGEN CONSUMPTION	CARDIAC OUTPUT PER MINUTE	OUTPUT PER BEAT	ARTERIAL-VENOUS DIFFERENCE	CARDIAC OUTPUT PER SQUARE METER	REMARKS
Case VIII. Hilda T. Unit No. 22523. Aged 25, female, height 168 cm.										
1929	*kgm.*				*cc. per minute*	*liters*	*cc.*	*cc. oxygen*		
January 16	55.7	98	106/54	+31	273	4.5	46	61	2.75	
January 19	55.9	99	106/54	+27	256	4.5	46	56	2.82	
						4.7	45			
January 22	56	98	102/50	+21	256	4.1	42	62	2.52	
January 25	56.3	90	104/58	+23	256	4.6	51	55	2.82	
						4.7	52			
January 28	57	93	104/54	+20	254	4.1	44	55	2.39	
						3.7	40			
February 2	57.1	93	110/58	+21	250	4.6	49	65	2.81	Patient sent home. Had had upper respiratory infection with irregular temperature for weeks
March 19	60	109	114/64	+37	294	5.3	48	54	3.26	
						5.4	49			Returned for operation, but looked ill and upper respiratory infection persisted
June 4	59.7	106	102/55	+20	260	4.0	38	64	2.41	
						4.1	38			Again returned for operation very much improved
June 18	59.5	90	105/60	−15	190	3.1	38	61	1.85	Operation, June 5, 1929
June 21		77	105/60	−23	166	2.7	35	59	1.67	
						2.9	38			

recorded by the house officer in the routine physical examination on admission to the hospital are compared with the blood pressure as determined when the cardiac output was measured (Table II).

The second point concerns the measurement of the work of the heart in hyperthyroidism. The current view among physiologists is that most of the work of the heart is measured by computing the product of the volume of blood driven out into the aorta and the

pressure to which it is raised. The kinetic energy involved, according to Starling's view, is comparatively small, although it becomes an appreciable increment when the output is greatly augmented and then may be as much as 15 per cent or more of the whole. Since the difference in blood pressure before and after treatment is very small, the difference in the cardiac output should then be a direct measure of the increased cardiac work. The work of the heart is increased at least to this amount. Thus in Otto K., for example, it may be estimated that the work of the heart, under basal resting conditions, was increased two to three-fold at the period when his thyroid intoxica-

TABLE II

Comparison of blood pressure readings on patients with hyperthyroidism: (a) during routine physical examination, (b) under basal conditions

PATIENT	NUMBER OF HISTORY	DATE	BLOOD PRESSURE DURING ROUTINE PHYSICAL EXAMINATION	BLOOD PRESSURE UNDER BASAL CONDITIONS
Harrison T.	23662	March 23	120/65	114/70
Otto K.	22093	December 8	112/60	114/78
Helen H.	22888	February 12	120/60	120/68
Edwin S.	23750	March 26	162/80	132/82
Anna K.	21808	November 23	152/74	150/82
Annie W.	21872	December 7	142/62	140/80
Viola J.	22870	February 5	130/50	124/68
Hilda T.	22523	January 16	115/55	106/54

tion was greatest. If the kinetic energy expended during the periods of increased output is still greater, then the work done may be still further augmented over that found in the normal resting condition.

An inspection of Table I will indicate the relation which exists between the metabolism, as measured by the oxygen consumption, and the cardiac output per minute. Where the basal metabolism was high the cardiac output was also increased. Any of the measures which were effective in lowering the basal metabolism were equally effective in reducing the cardiac output. The drop which followed operation was prompt, striking and lasting.

Such a prompt return to normal levels does not argue for permanent anatomical change in the heart. Cardiac enlargement as seen in x-ray photographs of patients with hyperthyroidism is fairly common (globular enlargement), and in several of these cases now reported slight diminution in the size of the heart shadow was discernible after treatment. It is often asserted that hypertrophy is common in hyperthyroidism, and it is suggested that this hypertrophy is a result of work, the action of the heart being compared to that of an individual who is constantly exercising. Such work hypertrophy has certainly not manifested itself in permanent changes in the minute output of the heart in the cases which we have studied here. Always with reduction of the rate of basal metabolism to normal there is a corresponding reduction in the cardiac output per minute.

There is an unmistakable tendency, in all of the subjects studied, for the output per beat to be high when the cardiac output per minute is increased and to diminish with the slowing of the minute volume. This increase in output per beat was also observed by Davies, Meakins and Sands.

Grollman has recently published data on the cardiac output of 51 normal subjects, 50 of whom were in the third decade of life. He found that the cardiac output was 2.2 $\pm$ 0.3 liters per minute per square meter of body surface and that the arterial-venous oxygen difference was 60 cc. $\pm$ 5 cc. per liter of blood in all of these normal subjects. The results of the study here reported indicate that the arterial-venous oxygen difference (oxygen utilization) tends to remain constant even when the basal metabolism and the cardiac output are markedly increased.

In untreated hyperthyroidism the cardiac output per minute per square meter of body surface is constantly increased over the normal values as found by Grollman, a natural consequence of the increased cardiac output with increased basal metabolic rate. This increase, calculated on the basis of surface area, drops to figures approximately in agreement with those of Grollman for normal persons when, following treatment, the increase in the basal metabolic rate has also disappeared. That close agreement, (*i.e.*, 2.2 $\pm$ 0.3 liters per minute per square meter of body surface), was not attained may be accounted for on two grounds: our patients were not of a restricted age group;

and the circulation, even at the time of the final test, may not have been yet restored to its normal equilibrium.

CONCLUSIONS

1. A parallelism is to be found between the increase in the basal metabolism and the cardiac output per minute in hyperthyroidism when the cardiac output is measured under basal conditions.

2. Only slight changes are found in the blood pressure of patients with hyperthyroidism before and after treatment. It is therefore probable that the increase in the cardiac output per minute is an approximate numerical measure of the increased work of the heart in this condition.

3. The fairly close relation which exists between elevation of metabolism and cardiac output in hyperthyroidism strongly suggests that the level of the metabolism in the disease is a factor of the first importance in the regulation of the cardiac output per minute under basal conditions.

CASE REPORTS

Case I. Harrison, T. (No. 23662). Male. Aged 60 years. Admitted March 14, 1929. Discharged May 2, 1929.

Had noticed an enlargement in the neck for twelve years. For the past year weakness, sweating and loss of weight with nervousness.

Physical findings: Loss of weight, exophthalmos with lid-lag, moist skin, tremor, diffusely enlarged thyroid gland. Slight cardiac enlargement, not confirmed by X-ray. Lungs clear.

Given Lugol's solution, 3 cc. daily, until April 26.

Double partial lobectomy April 27, from which he made an excellent recovery.

Case II. Otto K. (No. 22093). Male. Aged 39 years. Admitted December 5, 1928. Discharged January 9, 1929.

Onset with attack of nervousness while watching a soccer game on November 11, 1928. From that time on, he became easily tired, lost weight, had frequent night sweats, dyspnoea and palpitation. His eyes appeared shiny and larger.

Physical findings: Loss of weight, sweating hands, slight exophthalmos, lid-lag, enlarged thyroid, heart normal. Lungs clear.

Lugol's solution begun December 6th, up until operation, 3 cc. daily.

Transferred for operation on December 26th. Double partial lobectomy.

Recovery uneventful.

Case III. Helen H. (No. 22888). Female. Aged 30 years. Admitted January 29, 1929. Discharged March 10, 1929.

Onset two years ago with nervousness, mental fatiguability and irritability. One year ago dyspnoea on exertion and inability to use her hands well. Six months ago palpitation, night sweats, weakness, exophthalmos, hot flushes.

Physical findings: Tremor and enlarged thyroid. Slight cardiac enlargement, systolic murmur in pulmonic area. Rhythm regular. Lungs clear.

Lugol's solution started on February 4th, 3 cc. daily.

Operation February 19, 1929. Double partial lobectomy.

Discharged with basal metabolism at normal level and much improved.

Case IV. Edwin S. (No. 23750). Male. Aged 38 years. Admitted March 19, 1929. Discharged April 25, 1929.

Swelling of neck, prominence of eyes, nervousness, palpitation and shortness of breath, tremor and loss of weight. The symptoms were first noted two years ago and have gradually increased since.

Physical findings: Poorly nourished, apprehensive, moist skin, moderate exophthalmos, diffuse enlargement of thyroid gland. Slight cardiac enlargement to left with blowing systolic murmur. Lungs clear. Spleen palpable.

Given Lugol's solution, 3 cc. daily, until April 10.

Subtotal lobectomy, April 10, 1929.

Case V. Annie K. (No. 21808). Female. Aged 53 years. Admitted November 19, 1928. Died December 5, 1928.

Swelling of neck five years ago. Sometime later she became irritable and nervous, with tremor of hands. Two years ago she was obliged to stop work for two weeks on account of nervousness. One month ago she suddenly became very weak and was assisted home by friends. During past month three attacks of hysteria, crying spells. Neck has been getting larger, nervous tremor, loss of weight.

Physical findings: Enlarged thyroid, slight tremor of eyelids. Exophthalmos, tremor of fingers. Heart slightly enlarged, systolic murmur. Rhythm regular. Lungs clear.

Lugol's solution begun November 24th, 3 cc. daily, until operation.

Operation on December 5th, double partial lobectomy.

After operation she seemed in good condition, but at 8:00 p.m. her pulse was slightly irregular. 8:15—Complained of bandages being too tight. 8:30—Pulse was poor and she seemed unable to speak above a whisper. 8:45—Suddenly ceased to breathe. No autopsy.

Case VI. Annie W. (No. 21872). Female. Aged 44 years. Admitted November 22, 1928. Discharged January 9, 1929.

Weakness and fatiguability, with frontal headaches; most severe after exertion, for one year. Very nervous for past four months with tremor of right arm and hand. During past six months has had four or five attacks of night sweats and palpitation on exertion.

Physical findings: Staring eyes, loss of weight, moist skin, lid-lag, diffuse thyroid enlargement, slight enlargement of the heart with systolic murmur. Rhythm regular. Lungs clear.

Lugol's solution commenced November 28th, 3 cc. daily until operation.

Operation on December 19th, double partial lobectomy.

Recovery uneventful. Discharged in good condition.

Case VII. Viola J. (No. 22870). Female. Aged 25 years. Admitted January 28, 1929. Discharged March 15, 1929.

Onset two years ago with nervousness and irritability. One year ago palpitation of the heart after walking. Since April 1928 has had palpitation when excited or after talking a great deal. July 1928 had swelling of ankles and a friend called her attention to her enlarged neck. September 1928, increased appetite and thirst. For one month tremor of hands and hot flushes.

Physical findings: Tremor, sweats, slight exophthalmos. Loss of weight. Diffusely enlarged thyroid. Heart slightly enlarged, no murmurs, rhythm regular. Lungs clear.

Lugol's solution commenced February 4th, 3 cc. daily. Operation, February 18th, double partial lobectomy.

Recovery was uneventful and she was discharged in good condition.

Case VIII. Hilda T. (No. 22523). Female. Aged 25 years. Admitted January 3, 1929. Discharged February 7, 1929. Readmitted June 2, 1929. Discharged June 22, 1929.

A goiter noticed by school nurse four years ago. For the past year palpitation, nervousness, weakness and difficulty in breathing from the enlarged thyroid gland. Has taken several series of x-ray treatments, and Lugol's solution during the last three months of 1927.

Physical findings: Nervousness, tremor, sweating, flushing. Exophthalmos. Diffusely enlarged thyroid gland. Tachycardia. Heart slightly enlarged with soft systolic apical murmur.

During her first admission she developed influenza. Following recovery she was discharged for three months' rest. She returned for operation June 2, having taken 10 drops of Lugol's solution daily during the interim. At this time she felt improved, and was nervous only when fatigued. On physical examination there was nothing new made out. The thyroid gland was somewhat smaller and possibly somewhat more firm. A double partial lobectomy was done June 5 from which she recovered satisfactorily.

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